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-036
(102247)

March 2006

GlaxoSmithKline Biologicals

Study Title A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccinations.

Final Clinical Study Report for Study 102247 (rota-036)

(Development Phase IIIb)

INDICATION STUDIED: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.

Study Initiation Date:	08 September 2004
Date of the last Visit 5 (end of the 1st efficacy follow-up period):	07 September 2005
Data lock point for post Dose 3 immunogenicity of childhood vaccinations in Finland:	15 February 2006
Data lock point for post Dose 3 immunogenicity of childhood vaccinations in Italy:	28 February 2006
Date of report:	March 2006
Report scope:	This report presents final analyses of efficacy and safety objectives for the period from Dose 1 until end of the first efficacy follow-up period, immunogenicity of HRV vaccine and immunogenicity of childhood vaccines.

Sponsor Signatory: [redacted]
Clinical Research and Development
GlaxoSmithKline Biologicals

This study was performed in compliance with Good Clinical Practices including the archiving of essential documents.

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SYNOPSIS of Final Clinical Study Report for Study 102247 (rota-036)

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

Title of the study: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccinations.

Principal Investigators: This study was conducted by investigators in six European Union countries (Czech Republic, Finland, France, Germany, Italy and Spain).

Study Centers: Multicenter study. This study was conducted at multiple sites in six European Union countries (Czech Republic, Finland, France, Germany, Italy and Spain).

Publication (reference): Not published as of March 2006.

Study period: Study Initiation: 08 September 2004 Date of last Visit 5 (end of the 1st efficacy follow-up period): 07 September 2005 Data lock point for post Dose 3 immunogenicity of childhood vaccinations in Finland: 15 February 2006 Data lock point for post Dose 3 immunogenicity of childhood vaccinations in Italy: 28 February 2006	**Clinical phase:** IIIb

Objectives:

Primary objective

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any rotavirus (RV) gastroenteritis (GE) caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Secondary efficacy objectives for the first efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 type during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 types during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.

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

- To assess efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season. *(Note: This objective was not evaluated as the majority of subjects were vaccinated during the RV epidemic season)*

Secondary immunogenicity objectives (in the immunogenicity and reactogenicity subset, planned N=1800)

- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccinations.

Secondary reactogenicity and safety objectives

- In the immunogenicity and reactogenicity subset (planned N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited adverse events (AEs) (within 31 days after each dose) and serious adverse events during the entire course of the study.

Study design:

Randomized, double-blind, placebo-controlled, multi-country and multi-center study with two parallel groups: Group HRV vaccine and Group Placebo (control group). Subjects in each group were to receive two doses of HRV vaccine or placebo co-administered with the first two doses of the primary childhood vaccination series given according to the national plan of immunization in each country. Infanrix Hexa was co-administered with each HRV vaccine or placebo dose in each country, except in France where Infanrix Polio Hib was co-administered with the 2nd dose of HRV vaccine or placebo. Meningitec was co-administered in Spain, and Prevenar was co-administered in France and Germany. The third dose of the primary childhood vaccination series was to be administered according to the national plan of immunization in each country. Data collection was by remote data entry (RDE) using individual electronic case report forms (eCRF).

Number of subjects:

Enrolled and vaccinated: 3994 subjects (2646 in the HRV vaccine group and 1348 in the Placebo group)
Completed Visit 5: 3944 subjects (2613 in the HRV vaccine group and 1331 in the Placebo group)
Analyzed for safety: Total vaccinated cohort (primary safety analysis): 3994 subjects (2646 in the HRV vaccine group and 1348 in the Placebo group)
Analyzed for efficacy: According-to-Protocol (ATP) cohort for efficacy (primary efficacy analysis): 3874 subjects (2572 in the HRV vaccine group and 1302 in the Placebo group)
Analyzed for reactogenicity: Total vaccinated cohort for the immunogenicity and reactogenicity subset (primary reactogenicity analysis): 1404 subjects (914 in the HRV vaccine group and 490 in the Placebo group)
Analyzed for immunogenicity: ATP cohort for immunogenicity cohort (primary immunogenicity analysis): 1216 subjects (794 in the HRV vaccine group and 422 in the Placebo group)

Diagnosis and criteria for inclusion:

Healthy infants with birth weight > 2000g who were 6-14 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.

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

Study vaccine, dose, mode of administration, lot no.:

Vaccination schedule/site:

Lyophilized HRV vaccine was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose. Subjects received two doses according to 0, 1 to 2 months schedule.

Study Vaccine composition/ dose/ lot number:

One dose of GSK Biologicals' lyophilized HRV vaccine contained $10^{6.5}$ median Cell Culture Infective Dose (CCID50) of RIX4414 HRV strain derived from the 89-12 HRV vaccine strain, 3.7 mg Dulbecco's Modified Eagle Medium (DMEM), 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot number RVC018A42 was used for the HRV vaccine. Lot numbers DD05A003A and DD05A003C were used for the diluent (calcium carbonate 80 mg and xanthane 3.25 mg in 1.3 ml water for injection).

Reference vaccine, dose and mode of administration, lot no.:

Placebo schedule/site:

Lyophilized placebo was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose. Subjects received two doses according to 0, 1 to 2 months schedule.

Placebo composition/ dose/ lot number:

One dose of GSK Biologicals' lyophilized placebo contained 3.7 mg DMEM, 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot number RVC020A41PL was used for the placebo. Lot numbers DD05A003A and DD05A003C were used for the diluent (calcium carbonate 80 mg and xanthane 3.25 mg in 1.3 ml water for injection).

Duration of treatment:

The study duration from Visit 1 to Visit 5 at the end of the 1st efficacy period was approximately 8 months for each subject.

Criteria for evaluation of efficacy until Visit 5:

For each episode of GE (diarrhea with or without vomiting) occurring from Dose 1 up to Visit 5, a GE diary card was completed daily until end of GE symptoms. Collection of stool samples during each GE episode for RV detection by Enzyme Linked Immunosorbent Assay (ELISA) (RotaClone ELISA, Meridian Bioscience, USA). All stool samples that were RV positive were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridization assay at Delft Diagnostic Laboratory, the Netherlands to determine the G and the P types. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV. A 20-point scoring system was also used to assess the intensity of each GE episode (Ruuska T and Vesikari T, Scand J Infect Dis 1990;22:259–67). Score ≥11 on the Vesikari scale was defined as severe.

Primary endpoint:

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Secondary efficacy endpoints for the first efficacy follow-up period:

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 type during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 types during the first efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

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- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season. *(Note: This endpoint was not evaluated as almost all subjects were vaccinated during the RV epidemic season)*
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season. *(Note: This endpoint was not evaluated as almost all subjects were vaccinated during the RV epidemic season)*

Criteria for evaluation of immunogenicity:

In a subset of subjects: Collection of blood samples from subjects in the immunogenicity and reactogenicity subset at Visit 1 (all countries), Visit 3 (all countries), Visit 4 (only Spain) and Visit 6 (Finland and Italy).

Serum anti-rotavirus IgA antibody concentrations at Visit 1 and Visit 3 were measured using ELISA.

Serum levels of antibodies to all antigens contained in the co-administered childhood vaccinations were measured using standard assays at Visit 3 (all countries), Visit 4 (only Spain) and Visit 6 (only Finland and Italy).

Secondary immunogenicity endpoints (in a subset of subjects, planned N=1800):

- Serum rotavirus IgA antibody concentration expressed as geometric mean concentration (GMC) at Visit 1 and Visit 3.
- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccinations at Visit 3 and Visit 4:
  - Serum concentration/titer expressed as GMC/geometric mean titers (GMT) for antibodies to diphtheria, tetanus, Pertussis Toxoid (PT), Filamentous Haemagglutinin (FHA), Pertactin (PRN), poliovirus types 1, 2 and 3, Polyribosyl Ribitol Phosphate (PRP), Hepatitis B surface antigen (HBs), Serum bactericidal activity against *N. meningitidis* serogroup C (SBA-Men C), Polysaccharide C (PSC), and *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 International Units (IU)/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-poliovirus type 1 antibody titers ≥ 8
    - anti-poliovirus type 2 antibody titers ≥ 8
    - anti-poliovirus type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 µg/ml
    - anti-HBs antibody concentrations ≥ 10.0 milli International Units (mIU)/ml
  - Seropositivity status:
    - anti-PT antibody concentrations ≥ 5 ELISA Units (EL.U)/ml
    - anti-FHA antibody concentrations ≥ 5 EL.U/ml
    - anti-PRN antibody concentrations ≥ 5 EL.U/ml
    - anti-MenC antibody titer ≥ 1/8
    - anti-PSC antibody concentrations (ELISA) ≥ 0.3 µg/ml
    - antibody concentrations to Streptococcus *pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F ≥ 0.05 µg/ml

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

Criteria for evaluation of safety from Dose 1 until Visit 5:

In a subset of subjects: Recording of solicited symptoms (fever, fussiness/irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) from Day 0 to Day 7 after each dose of HRV vaccine/placebo.

In all subjects: Recording of unsolicited symptoms from Day 0 to Day 30 after each dose of HRV vaccine/placebo and serious adverse events (SAE) during the study period.

Secondary safety and reactogenicity endpoints:

- In a subset of subjects (planned N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccinations.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccinations, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- For all subjects, occurrence of SAEs throughout the entire study period.

Statistical methods:

Analyses were performed as per protocol and in a reporting and analysis plan.

Demography: The age at each vaccination and at Visit 5 were summarized by group using descriptive statistics. The gender and race composition, the distribution of enrolment between countries and the number of co-administered vaccines/ intercurrent vaccinations were summarized by group.

Analysis of efficacy: The first efficacy period was from 2 weeks after Dose 2 until Visit 5.

The duration of the first efficacy follow-up period was summarized by group. For each efficacy endpoint, the percentages of subjects reporting at least one episode were compared between groups using two-sided Fisher's exact test (significance level of α=0.05). The vaccine efficacy (VE) rate for each efficacy endpoint was calculated with its 95% CI. Exploratory VE was also calculated against each isolated RV type, severe RV GE with Clark score >16, by serological status for IgA antibody concentration at Visit 3, by feeding criteria, all cause GE, by country, all cause severe GE and hospitalization due to all cause GE.

Analysis of immunogenicity: At each time point that serum antibody response to a given antigen was measured, seroprotection/seroconversion/seropositivity rates and their exact 95% CI were calculated by group. GMCs/GMTs and their 95% CI were calculated by group. GMCs and their 95% CI were also calculated on the subjects who had seroconverted to anti-rotavirus IgA antibody.

The two-sided asymptotic standardized 95% CI for difference (HRV minus Placebo) in anti-rotavirus IgA seroconversion rates after one to two months after Dose 2 of HRV vaccine or placebo (Visit 3) was calculated.

The two-sided asymptotic standardized 95% CI for difference (Placebo minus HRV) in post Dose 2/Dose 3 seropositivity/seroprotection rates was calculated for each co-administered antigen by country.

The 95% CI for the ratio of post Dose 2/Dose 3 GMCs/GMTs (Placebo over HRV) was computed for each co-administered antigen by country (using a one-way ANOVA model on the logarithm10 transformation of the titers).

Analysis of reactogenicity and safety: The percentage of doses and of subjects with any symptom (solicited or unsolicited), with specific solicited symptoms (cough/runny nose, diarrhea, fever, fussiness/irritability, loss of appetite and vomiting) reported from Day 0 to Day 7 after any HRV vaccine/placebo dose were tabulated per group, along with exact 95% CI. The same calculations were done for symptoms rated as grade "3" in intensity and those assessed as related to vaccination. The differences between the HRV vaccine group and the Placebo group were explored for pooled countries using the two-sided Fisher's exact test (significant level of alpha = 0.05) for the percentage of subjects reporting each solicited symptom including those rated as grade 3 in intensity and those assessed as related to vaccination during the 8-day solicited follow-up period, after any HRV or placebo doses.

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The percentage of subjects with unsolicited symptoms reporting within 31 days were summarized by group, for pooled countries, according to the MedDRA SOC and PTs and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05). Similar tables were generated for grade 3 symptoms and for symptoms assessed as related to vaccination.

The percentage of subjects who reported an SAE/IS from Dose 1 of HRV vaccine or placebo up to Visit 5 were computed by group, for pooled countries, and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05). All SAEs and discontinuation due to AEs were tabulated by group.

The P-values were used as an aid to highlight potential imbalances worth further attention (significance level of alpha = 0.05) and care was to be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment, and the rate of false signals could be considerably large due to the number of comparisons. When a potential imbalance between groups was noted, individual AE cases were reviewed by a sponsor physician and conclusions were based on clinical judgement

Summary:

Demography Results: A total of 3994 subjects were enrolled in this study, with 72.4% of subjects enrolled in Finland.

ATP cohort for efficacy: For the pooled countries, the demographic profile (median age at each dose, distribution of male and female subjects and race) of the two groups was similar. There were more males than females: 52.7% males and 47.3% females. The median age at Dose 1 was 12.0 weeks and at Dose 2 was 20.0 weeks. The study population was predominantly White/Caucasian. The median age at Visit 5 was 11 months in both groups.

Efficacy results: Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) and the total vaccinated cohort. Mean duration of the first efficacy follow-up period (from two weeks after Dose 2 up to Visit 5) was 6 months in both groups.

Primary endpoint:

- Significantly fewer subjects in the HRV vaccine group reported any RV GE caused by the circulating wild-type RV compared to the Placebo group during the first efficacy follow-up period (P-value < 0.001). The primary endpoint was reached.

Secondary efficacy endpoints:

- During the first efficacy follow-up period, significantly fewer subjects in the HRV vaccine group reported severe RV GE caused by the circulating wild-type RV, any and severe RV GE episodes caused by G1 wild-type, any and severe RV GE episodes caused by non-G1 types, hospitalization for RV GE or medical attention for RV GE episodes compared to the Placebo group (P-value < 0.001 for each comparison).
- *From Dose 1 to Visit 5 (mean duration: 8 months in each study group):* VE against any RV GE caused by the circulating wild-type RV was 87.3% (95% CI: 80.3%; 92.0%), P-value < 0.001. VE against severe RV GE caused by the circulating wild-type RV was 96% (95% CI: 90.2%; 98.8%).
- *From Dose 1 to before Dose 2 (mean duration: [0]1.9 months in each study group)*: VE against any RV GE caused by the circulating wild-type RV was 89.8% (95% CI: 8.9%; 99.8%), P-value = 0.019.

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Table 1: Vaccine efficacy during the first efficacy follow-up period (ATP cohort for efficacy)

			n/N			Vaccine Efficacy			
				95% CI			95% CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Any RV GE due to circulating wild-type RV (Primary efficacy endpoint)									
HRV	2572	24	0.9	0.6	1.4	87.1	79.6	92.1	<0.001
Placebo	1302	94	7.2	5.9	8.8				
Severe* RV GE due to circulating wild-type RV									
HRV	2572	5	0.2	0.1	0.5	95.8	89.6	98.7	<0.001
Placebo	1302	60	4.6	3.5	5.9				
Any RV GE due to wild-type G1									
HRV	2572	4	0.2	0.0	0.4	95.6	87.9	98.8	<0.001
Placebo	1302	46	3.5	2.6	4.7				
Severe* RV GE due to wild-type G1									
HRV	2572	2	0.1	0.0	0.3	96.4	85.7	99.6	<0.001
Placebo	1302	28	2.2	1.4	3.1				
Any RV GE due to non-G1 types									
HRV	2572	20	0.8	0.5	1.2	79.3	64.6	88.4	<0.001
Placebo	1302	49	3.8	2.8	4.9				
Severe* RV GE due to non-G1 types									
HRV	2572	3	0.1	0.0	0.3	95.4	85.3	99.1	<0.001
Placebo	1302	33	2.5	1.8	3.5				
Hospitalization due to RV GE									
HRV	2572	0	0.0	0.0	0.1	100	81.8	100	<0.001
Placebo	1302	12	0.9	0.5	1.6				
RV GE requiring medical attention									
HRV	2572	10	0.4	0.2	0.7	91.8	84.0	96.3	<0.001
Placebo	1302	62	4.8	3.7	6.1				

*episodes with score ≥ 11 points on Vesikari scale

P-value = two-sided Fisher's exact test (significant level of α=0.05)

N = number of subjects included in each group

n/% = number/percentage of subjects with at least one specified RV GE episode reported in each group

95% CI,LL,UL = Lower and upper limits of the exact 95% confidence interval

Exploratory endpoints:

- VE against any RV GE caused by each isolated non-G1 types:
  - VE against any RV GE caused by G2 type was 62.0% (95% CI: -124.4%; 94.4%), P-value = 0.234.
  - VE against any RV GE caused by G3 type was 89.9% (95% CI: 9.5%; 99.8%), P-value = 0.018.
  - VE against any RV GE caused by G4 type was 88.3% (95% CI: 57.5%; 97.9%), P-value < 0.001.
  - VE against any RV GE caused by G9 type was 75.6% (95% CI: 51.1%; 88.5%), P-value < 0.001.
- VE against severe RV GE caused by each isolated non-G1 types:
  - VE against severe RV GE caused by G2 type was 74.7% (95% CI: -386.2%; 99.6%), P-value = 0.263.

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- VE against severe RV GE caused by G3 type was 100% (95% CI: 44.8%; 100%), P-value = 0.004.
- VE against severe RV GE caused by G4 type was 100% (95% CI: 64.9%; 100%), P-value < 0.001.
- VE against severe RV GE caused by G9 type was 94.7% (95% CI: 77.9%; 99.4%), P-value < 0.001.

- Observed VE against severe RV GE using the Clark scale was consistent with results using the Vesikari scale. The distribution of cases did however suggest differences between the Clark and Vesikari scale.
- In Finland, VE was 88.6% (95% CI: 81.0%; 93.4%) against any RV GE and 96.4% (95% CI: 90.2%; 99.1%) against severe RV GE, which is consistent with results for overall efficacy.
- An analysis by feeding criteria showed breast-feeding did not appear to have an impact on anti-rotavirus IgA response and VE. Since immunogenicity was evaluated only in a subset of subjects, it was not possible to correlate IgA seroconversion rate with VE
- Significantly fewer subjects in the HRV vaccine group reported severe all cause GE or GE requiring hospitalization compared to the Placebo group (P-value < 0.001 for each comparison). VE against severe all cause GE was 52.3% (95% CI: 38.0%; 63.3%). VE against all cause GE requiring hospitalization was 74.7% (95% CI: 45.5%; 88.9%).

Immunogenicity Results: Immunogenicity analysis was performed on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort for the immunogenicity and reactogenicity subset.

Immunogenicity of HRV vaccine

- Anti-rotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%) was observed in the HRV vaccine group at one to two months after Dose 2 of HRV vaccine or placebo.
- 6.7% (95% CI: 4.5%; 9.5%) subjects in the Placebo group were seropositive for anti-rotavirus IgA antibodies at one to two months after Dose 2 of HRV vaccine or placebo.
- The lower limit of the two-sided asymptotic standardized 95% CI for the difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody at one to two months after Dose 2 between the HRV vaccine group and (minus) the Placebo group was 76.2% indicating that the seroconverison rate was significantly higher in the HRV vaccine group as compared to the Placebo group.
- The observed IgA seroconversion rate in Finland seems to be higher than in the other countries. As this study was not designed to examine differences in IgA response between countries, valid conclusion can not be drawn. The differences between countries are likely due to different schedules used in different countries.

Immunogenicity of childhood vaccinations:

- **Post Dose 3 of childhood vaccines in Czech Republic, France Germany, and Spain:**
  - A high level of seroprotection rate /seropositivity rate to each childhood vaccine antigen was observed for both groups at post Dose 3 in each country, except for lower response in both groups in Germany. The lower response in Germany appeared to be limited to subjects enrolled at one particular center. A sub-analysis excluding that German center showed that immunogenicity was similarly high in Germany.
- For Czech Republic, France, Germany and Spain, a statistically significant difference was not detected between the two groups for post Dose 3 seropositivity rate /seroprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, 7 *Streptococcus pneumoniae* serotypes (France and Germany), and SBA-MenC and PSC (Spain) since the two-sided asymptotic standardized 95% CIs for the treatment differences (placebo minus HRV) contain

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

the value zero, except for anti-poliovirus type 2 antibody in Czech Republic (higher response for the HRV vaccine group)..

- For Czech Republic, France, Germany and Spain, a statistically significant difference was not detected between the two groups for post Dose 3 GMCs/GMTs of antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, 7 *Streptococcus pneumoniae* serotypes (France and Germany), and SBA-MenC and PSC (Spain) since the 95% CI for the ratios of GMC/GMT (placebo over HRV) for each antibody contain the value one.
- **Post Dose 2 of childhood vaccines in Finland, Italy and Spain:**
  - For Finland, Italy and Spain, a statistically significant difference was not detected between the two groups for post Dose 2 seropositivity rate /seroprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, and SBA-MenC and PSC (Spain) since the two-sided asymptotic standardized 95% CIs for the treatment differences (placebo minus HRV) contain the value zero, except for anti-PRP antibody in Finland (higher response for the HRV vaccine group).
  - For Finland, Italy and Spain, a statistically significant difference was not detected between the two groups for post Dose 2 GMC/GMT for antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, and SBA-MenC and PSC (Spain) since the 95% CI for the ratios of GMC/GMT (placebo over HRV) for each antibody contain the value one, except for anti-poliovirus type 3 antibody in Finland and in Spain (higher response for the HRV vaccine group)
- Post Dose 3 of childhood vaccines in Finland and Italy (interim analysis on total vaccinated cohort of the immunogenicity and reactogenicity subset in Finland and Italy): A high level of seroprotection rate /seropositivity rate to each childhood vaccine antigen was observed in both groups at post Dose 3 in Finland and Italy.

Reactogenicity and Safety Results:

Overall incidence of AEs: From Day 0 to Day 7 after any HRV vaccine/placebo doses, the percentages of subjects with any symptoms (solicited and unsolicited), including grade 3 and related AEs, were similar between the two groups.

Solicited AEs: Statistically significant differences were not detected between groups for the exploratory comparison between the HRV vaccine and Placebo groups for percentage of subjects with each specified solicited symptom (any, grade 3 and related) reported from Day 0 to Day 7 after any doses ($P > 0.05$).

Unsolicited AEs:

- Statistically significant differences were not detected between groups for the exploratory comparison between the HRV vaccine and Placebo groups with respect to the percentage of subjects with unsolicited AEs (any, grade 3 and related) reported from Day 0 to Day 30 after any HRV vaccine/placebo doses (two-sided Fisher's exact test were > 0.05 for each comparison).
- When unsolicited AEs from Day 0 to Day 30 after any HRV vaccine/placebo doses were classified according to the MedDRA SOCs/PTs, potential imbalance between the HRV vaccine group and the Placebo group was seen for the following AEs:
  - Potential imbalance in favour of the HRV vaccine was noted for diarrhea, stridor, grade 3 bronchiolitis, grade 3 otitis externa and grade 3 rhinorrhoea. All cases recovered/resolved completely except one case of grade 3 bronchiolitis which recovered/resolved with sequelae.
  - Potential imbalance in favour of the Placebo was noted for flatulence, irritability and irritability assessed as related to vaccination. All cases recovered completely.
  - Clinical review of individual cases by the sponsor physician gave no evidence of clinically relevant findings indicating that the potential imbalance was possibly a chance finding.

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

Serious Adverse Events: From Dose 1 of HRV vaccine/Placebo up to Visit 5, 5.5% (95% CI: 4.6%; 6.4%) subjects in HRV vaccine group and 7.0% (95% CI: 5.7%; 8.5%) subjects in the placebo reported at least one SAE (P-value = 0.049). No fatal events were reported up to Visit 5. Within the present trial setting, the vaccine was not associated with an increased risk of IS from Dose 1 up to Visit 5 compared to the placebo; the observed Risk Difference was 0.04% (95% CI: -0.25%; 0.21%, P-value = 0.457).
One case of intussusception (IS), assessed as related to vaccination, was reported 8 days after Dose 2 of HRV vaccine; the subject recovered completely. No more IS cases were reported during the follow-up period until Visit 5. No conclusions can be drawn on the basis of this single IS case observed up to Visit 5.
One case of non-RV GE reported 7 days after Dose 1 (SAE remains blinded) was assessed as related to vaccination; the subject recovered completely.
All other SAEs were assessed as not related to vaccination.
Withdrawals due to adverse events/serious adverse events: At Visit 5, four subjects were withdrawn due to unrelated non-fatal SAEs and nine subjects were withdrawn due to non-serious AEs. Of these, 5 AEs were assessed as related to vaccination and 4 were assessed as not related to vaccination.

Conclusions:

Efficacy

- Two oral doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccinations were highly effective compared to the placebo in protecting infants against any RV GE caused by the circulating wild-type RV during the first efficacy period. VE against any RV GE was **87.1%** (95% CI: **79.6%**; 92.1%). The primary objective of this study was met.
- Two oral doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccinations were highly effective during the first efficacy period compared to the placebo in protecting infants against:
  - Severe RV GE caused by the circulating wild-type RV; VE 95.8% (95% CI: 89.6%; 98.7%)
  - Any RV GE caused by G1 wild-type RV; VE 95.6% (95% CI: 87.9%; 98.8%)
  - Severe RV GE caused by G1 wild-type RVs; VE 96.4% (95% CI: 85.7%; 99.6%)
  - Any RV GE caused by non-G1 RV types; VE 79.3% (95% CI: 64.6%; 88.4%)
  - Severe RV GE caused by non-G1 RV types; VE 95.4% (95% CI: 85.3%; 99.1%)
  - Hospitalization due to RV GE caused by the circulating wild-type RV; VE 100% (95% CI: 81.8%; 100%)
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention; 91.8% (95% CI: 84.0%; 96.3%)
- Already after the first dose, GSK Biologicals' HRV vaccine was protective against any and severe RV GE caused by the circulating wild-type RV. VE against any RV GE was 89.8% (95% CI: 8.9%; 99.8%) during the period from Dose 1 to before Dose 2. VE estimates for the period from Dose 1 until Visit 5 were consistent with estimates for the first efficacy period.

Immunogenicity

- GSK Biologicals' HRV vaccine was immunogenic as shown by the anti-rotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%) observed in the HRV vaccine group at one to two months after Dose 2.
- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of any antigens contained in each of the co-administered childhood vaccinations (Infanrix Hexa, Infanrix Polio Hib, Prevenar or Meningitec).

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

Safety

- There was no evidence for a clinically meaningful difference between the HRV vaccine group and the Placebo group for SAEs reported from Dose 1 up to Visit 5 or unsolicited AEs reported within 31 days (Day 0 to Day 30) after each dose.
- The reactogenicity profile of two doses of HRV vaccine co-administered with childhood vaccinations was similar to that of the placebo in terms of the solicited symptoms reported within eight days (Day 0 to Day 7) after each dose.

Date of report: March 2006

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SUPPLEMENTS

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
BCG	Bacille Calmette-Guérin
BMI	Body Mass Index
CCID50	median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CI	Confidence Interval
DMEM	Dulbecco's Modified Eagle Medium
DTPa	Diphtheria and tetanus toxoids and acellular pertussis
eCRF	Electronic Case Report Form
ED50	50% Effective Dose
ELISA	Enzyme Linked ImmunoSorbent Assay
EL.U	Elisa Units
FHA	Filamentous haemagglutinin
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC/T	Geometric Mean Concentration/Titers
GSK	GlaxoSmithKline
HBs	Hepatitis B surface antigen
HBV	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IPV	Inactivated polio vaccine
IRB	Institutional Review Board
IS	Intussusception
IU	International Units
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
mIU	milli International Units
ml	milliliter
PID	Patient identification
PRN	Pertactin
PRP	Polyribosyl ribitol phosphate
PSC	Polysaccharide C
PT	Pertussis toxoid
RCC	Reverse Cumulative Distribution Curve
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SBA-MenC	Serum bactericidal activity against *N. meningitidis* serogroup C
SMS	Short Message Service
SOP	Standard Operating Procedures
U	Units
UL	Upper Limit
VE	Vaccine Efficacy
WRC-GCP	Worldwide Regulatory Compliance-GCP

COMMERCIAL VACCINES

Infanrix Hexa®	GSK Biologicals' combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated polio and *Haemophilus influenzae* type b vaccine
Infanrix Polio Hib®	GSK Biologicals' combined diphtheria and tetanus toxoids, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine
Prevenar®	Wyeth Pharmaceuticals' pneumococcal polysaccharide conjugate vaccine (7-valent)
Meningitec®	Wyeth Pharmaceuticals' meningococcal group C conjugate vaccine

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. Partially blind is to be used for study designs with different blinding levels between different groups, e.g. double blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study coordinator	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring proper conduct of a clinical study.
Completed:	Subject who complete the final study visit foreseen in the protocol. For this report, completed refers to a subject who completed Visit 5.
Diarrhea:	Passage of three or more looser than normal stools within a day.

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.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
First efficacy follow-up period:	Period starting from two weeks after Dose 2 of study vaccine or placebo and ending at Visit 5.
Gastroenteritis:	Diarrhea with or without vomiting.
Independent Data Monitoring Committee (IDMC):	The IDMC was responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical attention:	Medical provider contact, advice, visit; emergency room contact or visit or hospitalization.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Potential imbalance:	Two sided P-value <0.05 for group difference by two-sided test for the null hypothesis of identical incidence in both groups. (P-values less than 0.05 were used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment and clinical significance must be taken into account).
Protocol	Any change in a clinical protocol which affects the safety of subjects, the scope, design, assessments or scientific validity

amendment:	of the clinical investigation, e.g., dose change, duration of treatment, number of subjects, control group(s), the assessments.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Rotavirus gastroenteritis:	An episode of gastroenteritis occurring after Dose 1 of study vaccine or placebo 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 onset of the next gastroenteritis episode, if subject had several episodes of gastroenteritis were considered.
Rotavirus season:	The rotavirus epidemic season is expected from beginning of December to end of May in Europe.
SBIR:	A central randomization system on Internet.
Serious adverse event:	Any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, an important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition i.e intussusception.
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 units (U)/milliliter (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) seronegative for rotavirus.

Seronegative:	A subject with antibody concentration below the assay cut-off value.
Seropositive:	A subject with antibody concentration 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 (Vesikari scoring system).
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	Adverse events to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject(s):	Term used throughout the protocol to denote the enrolled individual(s), who participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Symptom sheet:	Specific pages in the individual case report form onto which the investigator transcribed from the diary card and/or other source documentation on solicited adverse event(s) reported by the subject/parents/guardians.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any adverse event reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, its amendment, informed consent and other information that required pre-approval were reviewed and approved by an investigational center IEC or IRB in each participating country.

Appendix 2A contains the study protocol and Appendix 2B the unique pages of the individual case report form used in the study. Details of IECs or IRBs are presented in Appendix 2C.

1.2. Ethical Conduct of the Study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including the Somerset West, 1996 version of the Declaration of Helsinki.

1.3. Subject Information and Consent

Written informed consent was obtained from each subject's parent/guardian before any study-specific procedures were performed.

Data collection was by remote data entry (RDE) using individual electronic case report forms (eCRF).

Representative copies of the Informed Consent Forms used in this study are provided in Appendix 2D.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

Prof. [redacted] at the [redacted] Finland, was identified as the principal coordinating investigator for this study as 72% of participating subjects were enrolled in Finland. As the principal coordinating investigator, Prof. [redacted] was designated to oversee this study and approve the study report.

This study was conducted by a total of 87 investigators / study coordinators in six countries: Czech Republic (14 investigators), Finland (12 investigators), France (21 investigators), Germany (26 investigators), Italy (2 investigators) and Spain (14 investigators).

Information regarding investigators responsible for the study in each participating country can be found in Appendix 2E. A brief *Curriculum Vitae* for each investigator is provided in Appendix 2F.

GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium was the study sponsor and was responsible for administration of the study including clinical trial supply management.

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician monitors the safety aspects of the human rotavirus (HRV) vaccine clinical development. In this capacity, the IDMC periodically reviewed safety data from this study.

3. INTRODUCTION

Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) among young children in both developed and developing countries. A recent review estimates that 611,000 (range 454,000–705,000) RV-related deaths occur in children under 5 years of age annually [Parashar , 2006]. Of these, 80% of the deaths are estimated in low-income countries of south Asia or sub-Saharan Africa. From 2000 to 2004, RV was estimated to cause 39% of hospitalizations for childhood diarrhea [Parashar , 2006].

Epidemiologic studies have shown that the estimated RV disease burden in different European countries is high [Johansen, 1999; Koopmans, 1999; Mrukowicz, 1999] and most of this burden is due to RV-associated hospitalization of young children. In Europe, the estimated RV associated hospitalization rates among children less than 5 years of age vary from 1 in 33 cases of RV infection in Finland, 1 in 54 in Sweden, 1 in 65 in Poland, 1 in 74 in the Netherlands and 1 in 80 in Spain [Gil, 2004].

Vaccination is considered as the most effective tool to control the global burden associated with RV GE.

Because of the history of causal relationship between intussusception (IS) and a previously licensed tetravalent rhesus human reassortant RV vaccine (RRV-TV or Rotashield™) [CDC, 1999; CDC, 1999; Murphy , 2001], exclusion of IS risk is a critical safety criterion for new RV vaccines. IS is a type of acute intestinal obstruction, which occurs when one segment of bowel becomes enfolded within another segment (often near ileo-cecal junction).

GSK Biologicals has produced an oral live attenuated HRV vaccine containing the RIX4414 vaccine strain. The HRV vaccine was developed from the 89-12 vaccine candidate which was well-tolerated, immunogenic and effective in the United States of America (USA) [Bernstein DI, 2002; Bernstein , 1999; Bernstein , 1998].

After initial dose-ranging trials [Vesikari , 2004], protective efficacy of two doses of the HRV vaccine was demonstrated against any and severe RV GE, as well as against hospitalization for RV GE in phase II studies in Finland [Vesikari, 2004], USA and Latin America (Brazil, Mexico and Venezuela) [Salinas , 2005]. Vaccine efficacy was

demonstrated against G1P[8] and G9P[8] RV [Vesikari, 2004; Salinas , 2005]. The HRV vaccine was well-tolerated and immunogenic in infants.

A large, multi-country phase III study was conducted to evaluate any potential risk for IS within 31 days after each of two oral doses of HRV vaccine and confirm vaccine efficacy (VE). 63,225 healthy infants from 11 Latin American countries and Finland received two oral doses of HRV vaccine or placebo at approximately 2 and 4 months of age and were actively followed for safety including IS for 1 to 2 months after Dose 2. The HRV vaccine was not associated with IS and proved highly effective against severe RV GE [Ruiz Palacios, 2006]. The observed risk estimate of -0.32/10,000 for IS during 31 days after HRV vaccination was not only below the initial risk increase of 4/10,000 that led to the withdrawal of RotaShield™ [Murphy , 2001; Kramarz, 2001] but was also below the subsequent consensus risk estimate of 1/10,000 for Rotashield™ [Peter, 2002; Murphy, 2003]. A subset of 20,169 infants from Latin America was followed for severe GE (severe GE was defined as episodes requiring hospitalization and/or rehydration per WHO treatment plan B or C). VE against severe RV GE and against RV associated-hospitalization was 85% ($P < 0.001$), reaching 100% against more severe RV GE. VE against the G1P[8] type was 91.8% (95%CI: 74.1%; 98.4%) and VE against non-G1 types (G2, G3, G4 and G9 types) was 75.4% (95%CI: 50.0%; 89.0%) respectively ($P < 0.001$). Hospitalization for diarrhea of any cause was reduced by 42% (95%CI: 29%; 53%, $P < 0.001$).

The co-administration of childhood vaccinations with the HRV vaccine has been studied in several trials [Salinas , 2005; Dennehy, 2005], and no immune interference between HRV vaccine and childhood vaccinations has been observed.

Continuing evaluation of the HRV vaccine, Study rota-036 was designed to evaluate the efficacy, immunogenicity, reactogenicity and safety of two doses of the HRV vaccine in healthy infants when co-administered with specific childhood vaccinations in the European setting. The immunogenicity of childhood vaccinations was also evaluated to explore any effect of co-administration with the HRV vaccine.

This report presents final analyses of efficacy and safety objectives for the period from Dose 1 until end of the first efficacy follow-up period, immunogenicity of HRV vaccine and immunogenicity of childhood vaccines. The post Dose 3 immunogenicity data for Finland and Italy presented in this report are results of interim analysis on the total vaccinated cohort. The final post Dose 3 immunogenicity data for Finland and Italy will be presented in an annex.

Efficacy and safety follow-up during the second efficacy follow-up period are ongoing. An annex report will present efficacy and safety follow-up data during the second efficacy period and efficacy data for the combined efficacy periods.

4. STUDY OBJECTIVES

The study objectives considered for analyses presented in this study report are listed below. Refer to the study protocol in Appendix 2A for all study objectives.

4.1. Primary objective

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

See Section 5.9.1 for the primary endpoint.

4.2. Secondary objectives

Secondary efficacy objectives for the first efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 type during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 types during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- To assess VE against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season. *(Note: This objective was not evaluated as the majority of subjects were vaccinated during the RV epidemic season; see Section 6.3.1)*

Secondary immunogenicity objectives (in the immunogenicity and reactogenicity subset, planned N=1800)

- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccinations.

Secondary reactogenicity and safety objectives

- In the immunogenicity and reactogenicity subset (planned N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited adverse events (AEs) (within 31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

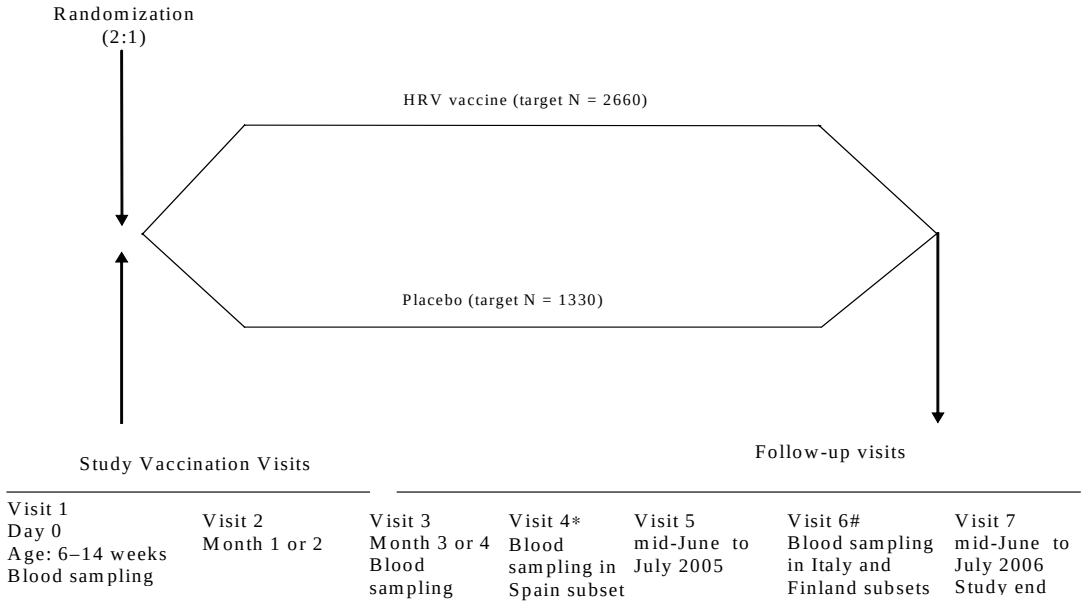
See Section 5.9.2 for secondary endpoints for the objectives listed above.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall Study Design – Description

Graphic presentation of the study design is presented below with planned enrolment numbers.



Blood sampling only in subjects who were part of the immunogenicity and reactogenicity subset
*At 7 months of age only for subjects in the immunogenicity and reactogenicity subset from Spain (optional).
#At 12 months of age only for subjects in the immunogenicity and reactogenicity subset from Italy (optional). At 13 months of age only for subjects in the immunogenicity and reactogenicity subset from Finland (optional).

This is a randomized, double-blind, placebo-controlled, multi-country and multi-center study conducted in Czech Republic, Finland, France, Germany, Italy and Spain. Eligible subjects were randomly assigned (2:1 randomization ratio) to one of the two parallel groups:

- Group HRV vaccine
- Group Placebo (control group)

Subjects in each group were to receive two doses of HRV vaccine or placebo co-administered with the first two doses of the primary childhood vaccination series given according to the national plan of immunization in each country. The third dose of the primary childhood vaccination series was to be administered according to the national plan of immunization in each country.

The vaccination schedules for childhood vaccinations primary series were as follows according to the national plan of immunization in each country:

Czech Republic	3, 4, 5 months of age
Finland	3, 5, 11-12 months of age
France and Germany	2, 3, 4 months of age
Italy	3, 5, 11 months of age
Spain	2, 4, 6 months of age

Data collection was by RDE using individual eCRFs.

The study duration from Visit 1 to Visit 5 at the end of the first efficacy follow-up period was approximately 8 months for each subject.

The total duration of the study (Visit 1 to Visit 7) will not exceed a total of maximum of 24 months per subject.

5.2. Study procedures

5.2.1. Outline of study procedures

Table 1 presents the study procedures at visits planned for all subjects in all countries.

Table 1 List of study procedures at visits planned for all subjects in all countries

Age Visit Timing Sampling timepoint	6-14 weeks VISIT 1 Day 0 Pre	VISIT 2 Month 1 or 2	VISIT 3 Month 3 or 4 Post vacc 2	VISIT 5	VISIT 7
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●‡		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in the immunogenicity and reactogenicity subset: for antibody determination	● (1 ml) (planned N=1800)		● (3 ml) (planned N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations*	●	●			
Recording all childhood vaccinations	●	●	●	● ***Finland and Italy only***	
Daily post-vaccination recording of solicited symptoms (Day 0-Day 7) by parents/guardians in a subset (N=1800 planned)	●	●			
Return of reactogenicity diary cards in a subset (N=1800 planned)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800 planned)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination	●	●	●	●	
Recording of unsolicited AEs within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●
Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

Shaded areas refer to study procedures after the data lock point for analyses presented in this report
The double-line border following Month 3 indicates the interim analysis which was performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.
● indicates a study procedure that requires documentation in the individual eCRF.
‡ Physical examination was to take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)
∗ The third dose of the childhood vaccine(s) was to be given according to the respective national Immunization plans of each country. A study visit was not planned specifically for administration of third dose of the childhood vaccine(s).
¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Subjects from Spain, Italy and Finland who were part of the "immunogenicity and reactogenicity subset" (planned N=300 per country) had, if necessary, an additional study visit because the blood sampling timepoint one month post Dose 3 of the childhood vaccinations in these countries did not coincide with study visits planned for all subjects.

Table 2 presents the study procedures at optional additional visits planned for planned for subjects in the immunogenicity and reactogenicity subset in Spain, Italy and Finland.

Table 2 List of study procedures at optional additional visits planned for subjects in the immunogenicity and reactogenicity subset in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6)

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2*	VISIT 6 FINLAND only Month 10 Post-vacc 2*	VISIT 6 ITALY only Month 9 Post-vacc 2*
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●‡	●‡	●‡
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in the immunogenicity and reactogenicity subset: for antibody determination (3 ml)	● (planned N=300 from Spain)	● (planned N=300 from Finland)	● (planned N=300 from Italy)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Day 0-Day 7) by parents/guardians in a subset (N=1800 planned)			
Return of reactogenicity diary cards in a subset (N=1800 planned)			
Transcription of the reactogenicity diary card in a subset (N=1800 planned)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination	●	●	●
Recording of unsolicited AEs within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

Shaded areas refer to study procedures after the data lock point for analyses presented in this report
● indicates a study procedure that requires documentation in the individual eCRF.
∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of childhood vaccinations.
‡ Physical examination was to take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)
¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Protocol-specified time intervals to be respected between visits are presented in Table 3.

Table 3 Protocol-specified intervals between study visits*

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine vaccination schedule	**3, 4, 5 months**	**3, 5, 11-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccinations
End of the 1st efficacy follow-up period (Visit 5)	Planned in mid-June to end-July 2005				
One month after the third dose of childhood vaccinations	Not applicable	30-48 days after the third dose of childhood vaccinations	Not applicable	30-48 days after the third dose of childhood vaccinations	Not applicable
End of the 2nd efficacy follow-up period (Visit 7)	Planned in mid-June to end-July 2006				

Shaded areas refer to study visits/contacts after the data lock point for analyses presented in this report
* = Date of the previous visit/contact was the reference date.

5.2.2. Intervals between Visit 1 and Visit 3 for inclusion in the According-to-Protocol (ATP) immunogenicity cohort

The protocol-specified intervals between Visit 1 and Visit 3 were adapted prior to analysis (see Table 4). These adapted intervals between Visit 1 and Visit 3 served as a criterion for inclusion or exclusion of subjects in the ATP cohort for immunogenicity analysis.

Table 4 Adapted intervals between Visits 1 and Visit 3 for inclusion in the ATP cohort for immunogenicity

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine vaccination schedule	**3, 4, 5 months**	**3, 5, 11-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	21-48 days	49-83 days	21-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	21-48 days	49-83 days	21-48 days	49-83 days

No subjects were eliminated from the ATP cohort for immunogenicity for not respecting intervals between other study visits, including the blood sampling visit after Dose 3 of childhood vaccinations.

5.3. Selection of study population

5.3.1. Inclusion criteria

All subjects had to satisfy the following criteria at study entry:

- Subjects who the investigator believed that their parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits and collection of stool samples) were to be enrolled in the study.
- A male or female between, and including, 6 and 14 weeks (42 – 104 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Birth weight > 2000g.

5.3.2. Exclusion criteria

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

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids were allowed.)
- History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B disease (in all subjects). Only for subjects in Spain: history of meningococcal group C disease.

Only for subjects in France and Germany: history of disease caused by *Streptococcus pneumoniae*.

- History of use of experimental RV vaccine.
- Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (in all subjects). Only for subjects in Spain: previous vaccination against meningococcal group C. Only for subjects in France and Germany: previous vaccination against *Streptococcus pneumoniae*.
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, IS or other medical condition determined to be serious by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at the time of enrolment. (Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).)
- GE within 7 days preceding the first study vaccine administration (warranted deferral of the vaccination).
- A family history of congenital or hereditary immunodeficiency.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- History of any neurologic disorders or seizures.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

5.3.3. Elimination criteria

The following criteria were checked at each visit subsequent to the first visit. If any became applicable during the study, it did not require withdrawal of the subject from the study but it determined a subject's evaluability in the ATP analysis.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids were allowed.)
- Administration of a vaccine 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 immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

5.3.4. Contraindications to subsequent doses of vaccine

5.3.4.1. Study vaccine

The following AEs constituted absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occurred during the study, the subject could not receive additional doses but could continue other study procedures at the discretion of the investigator. The subject was to be followed until resolution of the event, as with any AE (see Section 5.7.1):

- Hypersensitivity reaction due to the vaccine.
- 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 (see Section 5.2.1), or withdrawn at the discretion of the investigator. The subject was to be followed until resolution of the event, as with any AE (see Section 5.7.1).

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

5.3.4.2. Co-administered childhood vaccinations

DTP vaccines (including Infanrix Hexa and Infanrix Polio Hib)

The following AEs constituted absolute contraindications to further administration of DTP vaccine; if any of these AEs occurred during the study, the subject could not receive additional doses of vaccine but could continue other study procedures at the discretion of the investigator. The subject was to be followed until resolution of the event, as with any AE (see Section 5.7.1).

- Hypersensitivity reaction due to the vaccine.
- Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.

The following AEs constituted contraindications to administration of the study vaccine at that point in time; if any one of these AEs occurs 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 had to be followed until resolution of the event, as with any AE (see Section 5.7.1).

- Acute disease at the time of vaccination. (Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).
- Axillary temperature ≥37.5°C (99.5°F) / Rectal temperature ≥38°C (100.4°F) / Oral temperature ≥37.5°C (99.5°F).

Precautions:

- Fever of ≥40.5°C (rectal temperature) or ≥40.0°C (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 occurring within 48 hours of vaccination and lasting ≥ 3 hours.
- Seizures with or without fever occurring within 3 days of vaccination.

Meningitec

Absolute contraindications:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- Acute severe febrile illness.

Prevenar

Absolute contraindications:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- Acute severe febrile illness.

5.3.5. Subject completion and withdrawal from study

5.3.5.1. Subject withdrawal from the study

A withdrawal or drop-out was defined as any subject who did not come back for the concluding visit foreseen in the protocol. The investigator(s) attempted to contact those subjects who did not return for scheduled visits or follow-up. Information gathered was specified on the Study Conclusion page of the eCRF. The following possible reasons were responsible for withdrawal of the subject from the study:

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

For this report, drop-outs at Visit 5 were assessed.

5.4. Vaccines composition and administration

5.4.1. Description of Vaccines

5.4.1.1. Study vaccine

The HRV vaccine, placebo and diluent used in this study were developed and manufactured by GSK Biologicals, Rixensart, Belgium. The quality control standards and requirements for the vaccine are described in separate release protocols and the required approvals were obtained.

Table 5 presents the study vaccines' formulation and lot numbers used in the study.

Table 5 Vaccines, formulation and lot numbers

Vaccine	Formulation	Lot numbers
GSK Biologicals' HRV vaccine	RIX4414 HRV strain derived from the 89-12 HRV vaccine strain 106.5 median Cell Culture Infective Dose (CCID50) Dulbecco's Modified Eagle Medium (DMEM) 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	RVC018A42
GSK Biologicals' placebo	DMEM 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	RVC020A41PL
GSK Biologicals' diluent	Calcium carbonate 80 mg Xanthane 3.25 mg Water for injection q.s. ad 1.3 ml	DD05A003A and DD05A003C

5.4.1.2. Co-administered childhood vaccinations

Commercially available childhood vaccinations used in this study were:

- GSK Biologicals' Infanrix Hexa (combination vaccine containing diphtheria and tetanus toxoids and acellular pertussis (DTPa), Hepatitis B (HBV), *Haemophilus influenzae* type b (Hib) and Inactivated Polio vaccine (IPV))
- GSK Biologicals' Infanrix Polio Hib (combination vaccine containing DTPa, Hib and IPV)
- Wyeth Pharmaceuticals' Prevenar (7-valent pneumococcal polysaccharide conjugate vaccine)
- Wyeth Pharmaceuticals' Meningitec (meningococcal group C conjugate vaccine)

These commercial vaccines are assumed to have complied with the specifications given in the manufacturer's Summary of Product Characteristics.

5.4.2. Dosage and administration

- **Study vaccine**

  The HRV vaccine or placebo was prepared for administration by injecting the entire content of one pre-filled syringe containing the liquid diluent (calcium carbonate buffer) into the vial of the lyophilized product (HRV vaccine or placebo). The vial was shaken well to resuspend the lyophilized product. The entire volume of the resuspended product was withdrawn into the same syringe, the needle discarded and approximately 1 ml of the resuspended product was administered promptly as a single oral dose. If the subject regurgitated or vomited after study vaccine administration, no new study vaccine dose (HRV vaccine or placebo) was given at that visit. Regurgitation after vaccination did not lead to exclusion from any analyses.

- **Co-administered childhood vaccinations**

  Infanrix Hexa, Infanrix Polio Hib, Prevenar and Meningitec vaccines were prepared and administered according to the manufacturer's recommendations.

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

The study vaccine and co-administered childhood vaccinations were to be given according to the national plan of immunization schedule in each country. The vaccination regimen is summarized in Table 6.

Table 6 Dosage and administration

Country	Visit	Vaccination	Dose	Vaccine	Route	Site
Study vaccination						
All	1, 2	RV or placebo	1	HRV or placebo	O	not applicable
Co-administered childhood vaccination						
All, except France	1, 2	DTPa, HBV, IPV, Hib	1	Infanrix Hexa	IM	T
France	1	DTPa, HBV, IPV, Hib	1	Infanrix Hexa	IM	T
	2	DTPa, IPV, Hib	1	Infanrix Polio Hib	IM	T
France and Germany	1, 2	*Streptococcus pneumoniae*	1	Prevenar	IM	D/ T
Spain	1, 2	*Neisseria meningitidis* C	1	Meningitec	IM	D/ T

O = Oral IM = Intramuscular D = Deltoid T = Thigh

The third dose of the primary childhood vaccination series was to be administered according to the national plan of immunization in each country.

5.4.3. Treatment allocation and randomization

Planned enrolment was 3990 eligible subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the Placebo group).

A total of 2490 subjects were planned to be enrolled in Finland. A total of 300 subjects were planned to be enrolled in each of the remaining five countries (Czech Republic, France, Germany, Italy and Spain). In case a country lagged in subject recruitment, a redistribution of the planned enrolment numbers was to be considered to reach the total planned enrolment.

5.4.3.1. Randomization of supplies

A randomization list was generated at GSK Biologicals, Rixensart, Belgium using a standard SAS® (Statistical Analysis System) program and was used to number the vaccines. A blocking scheme randomization (2:1 ratio for vaccine : placebo) was used to ensure that balance between treatments was maintained: a single treatment number identified uniquely the vaccine doses to be administered to the same subject.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multicenter study, and to thus reduce the overall study recruitment period, an over-randomization of supplies was prepared.

The vaccine doses were to be distributed to each vaccination site while respecting the randomization block size.

5.4.3.2. Randomization of subjects

The treatment allocation at the investigator site was performed using a central randomization call-in system on Internet (SBIR). The randomization algorithm used a minimization procedure stratified by vaccination sites.

After confirmation that the subject was eligible, the person who was in charge of the vaccination accessed the randomization system on Internet. Upon providing a subject number for the subject, the randomization system used the minimization algorithm to determine the treatment number to be used for the subject. If Internet was not available, the subjects were administered the treatment number with the highest number still available at the vaccination site.

5.4.3.3. Subsets

A total of 1800 subjects (planned 300 subjects per country) were planned to be part of the immunogenicity and reactogenicity subset. Reactogenicity data and blood samples were collected from this subset to evaluate reactogenicity and immunogenicity. For Finland, 300 subjects enrolled at specific centers were to be part of the immunogenicity and reactogenicity subset. All of the 300 subjects planned to be enrolled in each of the other participating countries were to be part of this subset.

5.4.4. Blinding

This study is conducted in a double-blinded manner to allow unbiased evaluation of the HRV vaccine versus the placebo. The parents/guardians of the subjects, the study personnel including the study monitor and the investigator were unaware of the administered treatment.

No individual codes were held at the local GSK Biologicals' Safety Office or GSK Biologicals' Central Safety Office. The local GSK Biologicals' Safety Office was able to access the individual randomization code from the central randomization system on the Internet. The GSK Biologicals' Central Safety Office accessed the individual randomization code using Matex (a new randomization system at GSK). The code was broken by the Clinical Safety physician (Study Contact for Emergency Code Break in Sponsor Information page) only in the case of medical events that the investigator/physician in charge of the subject felt could not be treated without knowing the identity of the study vaccine(s). In the event that the code was broken, the reason was recorded in the eCRF and in the subject's medical record.

The IDMC had access to the individual codes and could decode the SAEs to identify the product administered to any subject and evaluate whether enrollment in the study needed to be halted during periodic review of SAEs.

During the analyses presented in this report, access to the individual treatment decode was limited to the statistician and the database administrator to maintain double blinding until study end.

5.4.5. Prior and concomitant medication/vaccinations

At each study visit/contact, the investigator questioned the subject's parents/guardian about any medication(s) taken.

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at any time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study vaccine (HRV vaccine or placebo) were to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever was later) were to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

All vaccines administered in the period beginning at birth and ending at the blood sampling visit after completion of the routine three-dose primary vaccination course were to be recorded with trade name, route of administration and date(s) of administration.

Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination was to recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for AEs was to be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment.

5.5. Assessment of efficacy variables

Follow-up of GE cases

GE was defined as diarrhea with or without vomiting. Active follow-up for occurrence of GE episodes was conducted starting from administration of Dose 1 of HRV vaccine or placebo until the last visit planned for each subject. The study staff made periodic contact with the subjects' parents/guardians to inquire about the occurrence of GE and any GE related medical care or advice, and hospitalization. This contact was by telephone, short message service (SMS) using cellular phone, an Independent Calling Center or another convenient means. All contacts were to be logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt was to be made before the next planned contact. The frequency of contacts was as follows.

Weekly contact

- From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005

- December 2005 to end of May 2006

Bi-weekly contact

- From June 2005 onwards until 1 December 2005
- June 2006 until study end

Data collection for GE cases

For each suspected GE episode occurring from Visit 1 to study end, a GE diary card was to be completed by the subject's parents/guardians daily until end of the GE episode. The following information was recorded on the GE diary card daily during each suspected GE episode:

- Axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject.
- Rehydration or other medication given to the subjects during the GE episode.
- Medical attention sought for each GE episode (medical personnel contact, advice, visit; emergency room contact or visit or hospitalization).
- Behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or any seizure).

The completed diary cards were to be returned to the investigator at the following study visit. The investigator verified the completed GE diary cards and transcribed the information into the appropriate sections of the eCRF, in English.

Assessment of intensity of GE episodes

The 20-point Vesikari scale

The information from the GE diary card was used to assess the intensity of the GE episodes using the 20-point Vesikari scale [Ruuska , 1990]. Based on the information in the GE diary card, points were assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, use of rehydration therapy or hospitalization for each episode of GE as shown in Table 7.

Table 7 The 20-point Vesikari scale to assess intensity of GE episodes

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode was scored.
§ missing confirmed corresponded to the situation where the route for temperature was omitted in the eCRF and had not been recovered while addressing queries to the investigator

For each episode of GE, a global score (sum of individual points) was calculated. The severity using the 20-points Vesikari scale was defined as below:

- A global score <7 was prospectively defined as mild,
- A global score between 7 and 10 was prospectively defined as moderate,
- A global score ≥11 was prospectively defined as severe [Ruuska , 1990].

Clark scale

The information from the GE diary card was also used to assess the intensity of the GE episodes using the 24-point Clark scoring system [Clark, 1988] for an exploratory evaluation. In this scale, points were assigned at GSK Biologicals according to duration and intensity of diarrhea, vomiting and fever, as well as on the intensity and duration of behavioral symptoms as shown in Table 8.

Table 8 The 24-point Clark scoring system to assess intensity of GE episodes

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode was scored.
§ Missing confirmed correspond to the situation where the route for temperature was omitted in the eCRF and had not been recovered while addressing queries to the investigator

For each episode of GE, a global score (sum of individual points) was calculated. The severity using the 24-points Clark scale was defined as below:

- A global score < 9 was prospectively defined as mild,
- A global score between 9 and 16 was prospectively defined as moderate,
- A global score > 16 was prospectively defined as severe.

Collection of stool samples during GE

For each suspected GE episode occurring during the study period, a stool sample was to be obtained from the subject. The stool sample was to be collected as soon as possible

after symptoms began but not later than 7 days after the onset of GE symptoms. Stool samples collected outside of the 7-day window were also to be submitted for analysis. The stool samples were to be stored preferably at refrigerator temperature (approximately 2-8°C) until they were transferred rapidly to the investigator's laboratory (within 0-3 days). In case a refrigerator was not available, samples could be kept at ambient temperature. The stool samples were stored frozen at approximately -20°C or colder until shipped to GSK Biologicals for analysis.

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 two timepoints either 7 days after the end of the GE episode or the day before onset of the next GE episode if subject had several episodes of GE were used to identify an episode of RV GE.

Analysis of GE stool samples

All GE stool samples were analyzed at GSK Biologicals, Rixensart, Belgium to detect RV antigen using Enzyme Linked Immunosorbent Assay (ELISA) (RotaClone assay from Meridian Bioscience, USA). If a stool sample tested positive for RV, the sample was to be tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridization assay at Delft Diagnostic Laboratory, the Netherlands to determine the G and P types. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV.

5.6. Assessment of immunogenicity variables

5.6.1. Laboratory assays and timepoints

Serum analysis

Whole blood samples were collected from subjects in the immunogenicity and reactogenicity subset at Visit 1 (all countries), Visit 3 (all countries), Visit 4 (only Spain) and Visit 6 (Finland and Italy). All blood samples were centrifuged, separated locally and shipped frozen to GSK Biologicals, Rixensart, Belgium. Sera were stored at -20°C until analysis was performed at GSK Biologicals, Rixensart, Belgium using standardized, validated procedures with adequate controls.

Serum anti-rotavirus IgA antibody concentrations were measured at Visits 1 and 3 using an in-house ELISA test adapted from the assay developed by Ward et al [Ward, 1989]. Although not requested by the protocol, serum anti-rotavirus IgA antibody concentrations were also measured at Visit 4 in Spain. The antibody concentrations were expressed in units per milliliter (U/ml) and the assay cut-off was 20 U/ml. 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.

Serum levels of antibodies to antigens contained in the co-administered childhood vaccinations were measured using standard assays at Visit 3 (all countries), Visit 4 (only Spain) and Visit 6 (only Finland and Italy).

Table 9 summarizes the laboratory assays performed on serum samples.

Table 9 Serological assays

Antibody	Assay method	Test Kit/ Manufacturer	Assay cut-off	References
All countries				
Anti-rotavirus IgA	IgA ELISA	in-house	20 U/ml	[Ward, 1989]
Anti-D	ELISA	in-house	0.1 IU/ml†	[Camargo, 1984]
Anti-T	ELISA	in-house	0.1 IU/ml†	[Melville-Smith, 1983]
Anti-PT	ELISA	in-house	5 EL.U/ml	[Granstorm, 1987; Karpinsky, 1987]
Anti-FHA	ELISA	in-house	5 EL.U/ml	
Anti-PRN	ELISA	in-house	5 EL.U/ml	
Anti-HBs	ELISA	in-house	10 mIU/ml†	
Anti-poliovirus type 1	Micro-neutralization test	in-house	1:8 ED50†	[WHO, 1996]
Anti-poliovirus type 2	Micro-neutralization test	in-house	1:8 ED50†	
Anti-poliovirus type 3	Micro-neutralization test	in-house	1:8 ED50†	
Anti-PRP	ELISA	in-house	0.15 µg/ml†	[Eskola, 1999]
Spain				
SBA-MenC	Serum bactericidal test	in-house	1:8 Dilution	[Maslanka, 1997; Andrews, 2003; Borrow, 2001]
Anti-PSC	ELISA	In-house	0.3 µg/ml	[Amato Neto, 1974; Gheesling, 1994]
France and Germany				
Antibodies against *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23 F 7 capsular polysaccharide	ELISA	in-house	0.05 µg/ml	

†Seroprotective level
D = Diphtheria toxoid T = Tetanus toxoid
PT = Pertussis toxoid FHA = Filamentous haemagglutinin PRN = Pertactin
HBs = Hepatitis B surface antigen
PRP = Polyribosyl ribitol phosphate
SBA MenC = Serum bactericidal activity against *N. meningitidis* serogroup C
PSC = Polysaccharide C
U = Units IU = International Units
EL.U = Elisa Units ED50 = 50% Effective Dose

Table 10 presents the serology plan.

Table 10 Serology plan

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	Month	Visit no			
Pre	0	1	HRV	Immunogenicity subset all countries	none
Post-vacc 2∗	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP, 7 S. pneumoniae serotypes (France and Germany only)	Immunogenicity subset all countries except Spain	HRV, 7 S. pneumoniae serotypes (France and Germany only), D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP.
	4	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test	Immunogenicity subset from Spain	HRV, SBA-MenC, PSC, D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP.
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test	Immunogenicity subset from Spain	SBA-MenC, PSC, D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP.
	10	6 (Finland and Italy)	D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP	Immunogenicity subset from Finland and Italy	D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP

Although not planned, antibodies to HRV were also measured at Visit 5 for Spain.

∗ Post Dose 2 of HRV vaccine or placebo for all countries. Post Dose 3 of co-administered childhood vaccinations in Czech Republic, France and Germany. Post Dose 2 of childhood vaccinations in Finland, Italy and Spain.

Post Dose 3 of childhood vaccinations in Spain and Finland.

5.7. Assessment of safety variables

5.7.1. Adverse events

Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study procedure) were recorded in the medical history section of the subject's eCRF.

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

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.

An AE was defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The investigator inquired about the occurrence of AEs/SAEs at every visit/contact during the study. All AEs either observed by the investigator or one of his clinical collaborators or reported by the subject's parent/guardian spontaneously or in response to a direct question were evaluated by the investigator. As a consistent method of soliciting AEs, the subject's parent/guardian were 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?" AEs not previously documented in the study were recorded in the Adverse Event form within the subject's eCRF irrespective of severity or whether or not they are considered vaccination-related. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination were established. Details of any corrective treatment were recorded on the appropriate page of the eCRF.

Any medical attention sought for each solicited and unsolicited symptom was recorded in the eCRF. Medical attention was defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor).

Investigators followed-up subjects

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event had resolved, subsided, stabilized, disappeared, the event was otherwise explained, or the subject was lost to follow-up

- or, in the case of other non-serious AEs (unsolicited symptoms), until they completed the study or they were lost to follow-up.

AEs already documented in the eCRF, i.e. at a previous assessment, and designated as "not recovered/not resolved" or "recovering/resolving" were reviewed at subsequent visits, as necessary. If these had resolved, the documentation in the eCRF was completed. If an AE changed in frequency or intensity during the specified reporting period, a new record of the event was entered.

When an AE leading to drop out/SAE occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator recorded all relevant information on the eCRF or SAE Report Form as applicable. The investigator attempted to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, ultrasound etc.) that were judged by the investigator to be clinically significant were recorded as AEs or SAEs if they met the definition of an AE, as defined in Section 5.7.1 or SAE, as defined in Section 5.7.3. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were reported as AEs or SAEs. The investigator exercised his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant. Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided.

Assessment of AEs

- Diary cards were provided to the parents/guardians of all subjects to record unsolicited AEs (except GE) and medications taken between Visit 1 and Visit 3. The completed diary cards were to be returned to the investigator at the following study visit. The investigator verified the completed diary cards and recorded AEs occurring within 31 days (Day 0-Day 31) after each dose of HRV vaccine or placebo as "unsolicited symptoms" on the Adverse Event form in the subject's eCRF.

- All AEs leading to subject withdrawal or drop out were recorded on the Adverse Event form in the subject's eCRF.

- All SAEs during the entire study period were recorded in the SAE Report Form. See Section 5.7.3 for definition and reporting of SAEs.

- Solicited symptoms occurring during eight days (Day 0 to Day 7) after each HRV vaccine or placebo dose were assessed in subjects who were part of the immunogenicity and reactogenicity subset. See Section 5.7.2 for assessment of solicited symptoms.

A post-study AE/SAE was defined as any event that occurs outside of the AE/SAE detection period defined above. Investigators were not obligated to actively seek AEs or SAEs in former study participants.

Intensity of unsolicited symptoms, AEs leading to drop out and SAEs

Based on their clinical judgement, the investigators assessed intensity of the reported unsolicited symptoms, AEs leading to drop out and SAEs, as follows:

1 (mild)	=	An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevented normal, everyday activities. (In a young child, such an AE would, for example, prevented attendance at a day-care center and caused the parents/ guardians to seek medical advice)

Relationship between vaccination and solicited symptoms, unsolicited symptoms, AEs leading to drop out and SAEs

The investigators assessed the relationship between investigational product and the occurrence of each event using their clinical judgement.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered.

The investigator therefore assessed whether the AE could be causally related to vaccination rather than to the individual vaccines.

Causality of all AEs was assessed by the investigator using the following question: Was there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	The AE was not causally related to administration of the study vaccine(s). There were other, more likely causes and administration of the study vaccine(s) was not suspected to have contributed to the AE.
YES	:	There was a reasonable possibility that the vaccine(s) contributed to the AE.

GSK Biologicals could request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE leading to drop-out or SAE. The investigator was obliged to assist.

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined "serious" (see Section 5.7.3 for definition of 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

Outcome

Outcome of unsolicited symptoms, AE leading to drop out or SAE reported during the study was assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (for SAEs only).

5.7.2. Solicited symptoms only in the immunogenicity and reactogenicity subset

Parents/guardians of subjects who were part of the immunogenicity and reactogenicity subset (planned 300 subjects per country) were provided with Reactogenicity Diary Cards to record information on solicited symptoms specified in Table 11 during eight days (Day 0 to Day 7) after each HRV vaccine or placebo dose.

Table 11 Solicited general adverse events

Fever (Rectal/Axillary)
Fussiness/Irritability
Loss of appetite
Vomiting
Diarrhea
Cough/runny nose

Fever was defined as temperature ≥38°C (≥37.5°C) as measured by a rectal (axillary) thermometer. Temperature was to be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature was to be recorded.
Diarrhea was defined as passage of three or more, looser than normal stools within a day.
Vomiting was defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

The intensity of any fussiness/irritability, loss of appetite or cough/runny nose was noted by parents/guardians according to the intensity scale described in Table 12.

Table 12 Intensity scales to be used by parents/guardians for solicited symptoms reported during the 8-day (Day 0 to Day 7) solicited follow-up period after each HRV vaccine/placebo dose

Adverse Experience	Intensity grade	Parameter
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
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

Parents/guardians recorded the temperature in °C using a rectal/axillary thermometer and the number of looser than normal stools and vomiting episodes. The maximum intensity of fever, diarrhea and vomiting occurring during the solicited 8-day follow-up period was scored at GSK Biologicals using the scale shown in Table 13.

Table 13 Intensity scales used at GSK Biologicals for fever, diarrhea, and vomiting reported during the 8-day (Day 0 to Day 7) solicited follow-up period after each HRV vaccine/placebo dose

Adverse Experience	Intensity grade	Parameter
Fever	0	Rectal temperature < 38.0°C or axillary temperature < 37.5°C
	1	Rectal temperature ≥ 38.0°C – ≤ 38.5°C or axillary temperature ≥ 37.5°C – ≤ 38.0°C
	2	Rectal temperature > 38.5°C – ≤ 39.5°C or axillary temperature > 38.0°C – ≤ 39.0°C
	3	Rectal temperature > 39.5°C or axillary temperature > 39.0°C
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

Parents/guardians were to return the completed Reactogenicity Diary Cards to the investigator at the following study visit. The investigators verified the completed Reactogenicity Diary Cards and transcribed the information into the appropriate sections of the eCRF, in English.

Relationship of solicited symptoms to vaccination was assessed as described in Section 5.7.1.

5.7.3. Serious adverse events

A SAE was any untoward medical occurrence that

a. resulted in death,

b. was life-threatening,

c. required hospitalization or prolongation of existing hospitalization,

d. resulted in disability/incapacity,

e. was a congenital anomaly/birth defect in the offspring of a study subject,

f. medical or scientific judgement was exercised in deciding whether reporting was appropriate in other situations, such as important medical events i.e. IS that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

The follow-up of SAEs was performed for all subjects starting from administration of Dose 1 onwards throughout the entire study period. SAEs that were related to study

participation (e.g. procedures, invasive tests, and a change from existing therapy) or were related to a concurrent medication were to be collected and recorded from the time the subject's parents consented to participate in the study until she/he was discharged.

The investigator inquired about the occurrence of SAEs at every visit/contact during the study. SAEs were to be reported promptly to GSK once the investigator determined that the event met the protocol definition of an SAE. The investigator or designate faxed the SAE reports to GSK Biologicals' Study Contact for reporting SAEs within 24 hours of his/her becoming aware of these events. Additional or follow-up information relating to the initial SAE report was also to be reported to the GSK Biologicals' Study Contact for reporting SAEs within 24 hours of receipt of such information. The investigator provided an assessment of causality, as described in Section 5.7.1, at the time of the initial report. In the event of a death determined by the investigator to be related to vaccination, sending of the fax was to be accompanied by telephone call to the Study Contact for reporting SAEs. If a subject died during participation in the study or during a recognized follow-up period, GSK Biologicals was to be provided with a copy of any available post-mortem findings, including histopathology.

Investigator safety reports were prepared for each SAE according to the current GSK policy and were forwarded to investigators as necessary. An investigator safety report was prepared for a SAE(s) that was both attributable to investigational product and unexpected. The purpose of the report was to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

If an investigator learnt of any SAE, including a death, at any time after a subject had been discharged from the study, and he/she considered the event reasonably related to the investigational product, the investigator was to promptly notify the Study Contact for reporting SAEs.

5.7.3.1. Intussusception

The investigators were required to inform the subject's parents/guardians of the signs and symptoms of IS (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C). Parents/guardians/caretakers of study subjects were instructed to seek medical advice at the nearest hospital in case of symptoms indicative of IS, and to inform the investigator. The investigator and his staff were to take appropriate actions to treat the condition.

The investigators were asked to follow the same procedures for reporting IS cases as for other SAEs. The diagnosis of IS was to be documented by radiography. Documentation by ultrasonography was optional depending on availability of necessary expertise. In addition to the SAE Report Form, an IS Form was also completed for each IS case.

Several biological samples (stool samples (rectal swabs if stool samples not available), throat swabs, blood samples (acute and convalescent sera), and surgical specimens if surgical resection was performed) were to be collected at the treatment site for all IS cases. Tests to be performed on the IS samples were specified in the protocol.

In light of results from the large phase III study rota-023 that established the safety of GSK Biologicals' HRV vaccine with respect to definite IS [Ruiz Palacios, 2006], the sponsor decided that testing of the IS samples collected during study rota-036 would be performed only if requested by the Regulatory Authorities. Biological samples collected from IS cases during the present study are being stored at GSK Biologicals, Rixensart, Belgium.

5.8. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, eCRF and safety reporting were reviewed with the investigator and his/her personnel responsible for the conduct of the study by the Company representative(s) 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 and source data/documents. All procedures were performed according to methodologies detailed in GSK Biologicals Standard Operating Procedures (SOPs).

Independent Audit statement:

- This study was subject to audits by GSK's department of Worldwide Regulatory Compliance-GCP (WRC-GCP). Audit certificates are provided in Study Information Appendix 2H.

5.9. Statistical methods for analysis of efficacy, safety and immunogenicity

The statistical methods for analyses of study objectives considered for this study report are described.

All statistical analyses were generated by GSK Biologicals, Belgium as planned in the protocol and in a reporting and analysis plan finalized on 03 November 2005 except for changes described in Section 5.10.2. The analyses were performed using SAS 8.2 and Proc StatXact-5 on Windows NT 4.

5.9.1. Primary efficacy endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

5.9.2. Secondary endpoints

Secondary efficacy endpoints during the first efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 type during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 types during the first efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season. *(Note: This endpoint was not evaluated as almost all subjects were vaccinated during the RV epidemic season)*
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season. *(Note: This endpoint was not evaluated as almost all subjects were vaccinated during the RV epidemic season)*

Secondary immunogenicity endpoints (in a subset of subjects, planned N=1800)

- Serum rotavirus IgA antibody concentration expressed as geometric mean concentration (GMC) at Visit 1 and Visit 3.
- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3. Refer to the glossary of terms for definition of seroconversion.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccinations at Visit 3 and Visit 4:
    - Serum concentration/titer expressed as GMC/geometric mean titer (GMT) for antibodies to diphtheria, tetanus, PT, FHA, PRN, poliovirus types 1, 2 and 3, PRP, HBs, Men C, PSC, and Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.
    - Seroprotection status:
        - anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
        - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
        - anti-poliovirus type 1 antibody titers ≥ 8
        - anti-poliovirus type 2 antibody titers ≥ 8
        - anti-poliovirus type 3 antibody titers ≥ 8
        - anti-PRP antibody concentrations ≥ 0.15 μg/ml and ≥ 1.0 μg/ml
        - anti-HBs antibody concentrations ≥ 10.0 mIU/ml

- Seropositivity status:
  - anti-PT antibody concentrations ≥ 5 EL.U/ml
  - anti-FHA antibody concentrations ≥ 5 EL.U/ml
  - anti-PRN antibody concentrations ≥ 5 EL.U/ml
  - anti-MenC antibody titer ≥ 1/8
  - anti-PSC antibody concentrations (ELISA) ≥ 0.3 µg/ml
  - antibody concentrations to Streptococcus *pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F ≥ 0.05 µg/ml

Secondary safety and reactogenicity endpoints

- In a subset of subjects (planned N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccinations.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccinations, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- For all subjects, occurrence of SAEs throughout the entire study period.

Refer to the study protocol in Appendix 2A for all study endpoints.

5.9.3. Determination of sample size for efficacy evaluation

The planned sample size in this study was 3990 enrolled subjects to be randomized in a 2:1 ratio to receive either the HRV vaccine or the placebo. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 3 390 subjects (2260 in the HRV vaccine group and 1130 in the Placebo group) were expected to be evaluable for the analysis of the primary objective.

Considering a 2:1 randomization ratio and various incidence rates, Table 14 provides the power for the 95% CI of the VE against any RV GE (primary endpoint) to be above given limits. Based on the results from Study rota-004 in Finland, an incidence rate of 10% for the percentage of placebo recipients with any RV GE caused by the circulating wild-type RV strains during the first efficacy period was considered as a reasonable assumption. Therefore if the VE was truly 70%, the study had at least 90% power to observe a 95% CI for the VE that would be above 50%.

Table 14 Power to observe a 95% CI above various cut-offs according to various incidence rates and true VE (power obtained from simulations using 2260 evaluable subjects in the HRV vaccine group and 1130 evaluable subjects in the Placebo group)

Incidence rate in the placebo	True VE	Cut-off for the lower limit of the 95% CI on VE					
		0%	10%	20%	30%	40%	50%
Any GE							
10%*	70% 60%	100% 100%	100% 100%	100% 100%	100% 97%	100% 81%	91% 32%
8%	70% 60%	100% 100%	100% 100%	100% 99%	100% 94%	98% 73%	82% 29%
6%	70% 60%	100% 100%	100% 99%	100% 96%	99% 85%	93% 60%	71% 21%
Severe GE							
4%*	80% 70%	100% 100%	100% 99%	100% 98%	99% 93%	98% 81%	92% 53%
3%	80% 70%	100% 98%	99% 97%	99% 93%	97% 85%	93% 68%	80% 40%
2%	80% 70%	98% 92%	97% 86%	94% 78%	90% 64%	80% 46%	60% 26%

*anticipated incidence rate

Using an estimation of the seroprotection rates of 97% for anti-diphtheria, of 99% for anti-tetanus, of 100% for anti-PRP, of 94% for anti-HBs, of 100% for anti-poliovirus type 1, 2 and 3 antibodies and a standard deviation between 0.28 to 0.33 for anti-PT, anti-FHA, anti-PRN antibody concentrations (reference study: rota-007), and assuming that the rates / GMC were the same in the HRV vaccine group and the Placebo group, a subset of 160 evaluable subjects in the HRV vaccine group and 80 in the Placebo group was estimated to provide at least 80% global power that all the 95% CIs on the decrease in seroprotection rates with the HRV vaccine group as compared to the Placebo group were below 10% and that the 95% CIs on the fold decrease in anti-PT, anti-FHA, anti-PRN GMCs with the HRV vaccine group as compared to the Placebo group was below 1.5 (using PASS 2000 for the difference in seroprotection rates and using Nquery for the ratio of anti-PT, anti-FHA, anti-PRN GMCs, one sided equivalence test, alpha=2.5%). These analyses were exploratory. Allowing for up to 20% of subjects who might not be evaluable for the immunogenicity analysis, 300 subjects were planned to be sampled by country.

5.9.4. Study cohorts/data sets analyzed

Total vaccinated cohort

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

- a safety analysis based on the total vaccinated cohort included all vaccinated subjects.
- an efficacy analysis based on the total vaccinated cohort included all vaccinated subjects.

Total Vaccinated cohort for the immunogenicity and reactogenicity subset

The total vaccinated cohort for the immunogenicity and reactogenicity subset included all subjects with at least one study vaccine administration documented and for whom solicited symptoms and blood samples were to be collected:

- a reactogenicity analysis based on the total vaccinated cohort for the immunogenicity and reactogenicity subset included all vaccinated subjects for whom solicited symptoms were to be collected.
- an immunogenicity analysis based on the total vaccinated cohort for the immunogenicity and reactogenicity subset included all vaccinated subjects for whom immunogenicity data were available.

ATP cohort for efficacy

The ATP cohort for efficacy included all subjects:

- who received 2 doses of HRV vaccine or placebo according to their random assignment,
- who had entered into the efficacy surveillance period: had follow-up beyond 2 weeks after Dose 2 of study vaccination for the analysis of the first efficacy follow-up period,
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 was administered and 2 weeks after Dose 2 of HRV vaccine or placebo was administered,
- for whom the randomization code had not been broken,
- who had not received a vaccine forbidden by or not specified in the protocol,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1 of HRV vaccine or placebo for subjects included in the immunogenicity and reactogenicity subset,
- who had not received a replacement vial, except if the appropriate vaccine was administered in double-blind replacement.

ATP cohort for reactogenicity

The ATP cohort for reactogenicity included all vaccinated subjects for whom solicited symptoms were to be collected and

- who had received at least one dose of study vaccine/control according to their random assignment,
- for whom the randomization code had not been broken,
- who had not received a replacement vial, except if the appropriate vaccine was administered in “double-blind replacement”,
- who had not received a vaccine forbidden by or not specified in the protocol,

- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1 of HRV vaccine or placebo.

ATP cohort for immunogenicity

The ATP cohort for immunogenicity included all subjects from the ATP cohort for reactogenicity:

- 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 for HRV vaccine or placebo,
- who complied with blood sampling schedule (i.e. respected time intervals for blood sampling visits mentioned in Table 4),
- for whom immunogenicity data were available, at pre and post sampling timepoint for anti-rotavirus IgA antibody.
- who had no RV other than vaccine strain in GE stool samples collected up to Visit 3.
- who had no concomitant infection unrelated to the vaccine which might influence the immune response.

Analyzed cohorts

The ATP cohort for efficacy was used for the primary analysis of efficacy. A secondary analysis of efficacy based on the total vaccinated cohort was also performed.

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

The total vaccinated cohort for immunogenicity and reactogenicity subset was used for the primary analysis of reactogenicity. Unsolicited AEs were presented for the total vaccinated cohort. The analysis on the ATP cohort for reactogenicity was to be performed only if more than 5% of the subjects from the total vaccinated cohort for immunogenicity and reactogenicity subset were excluded from the ATP cohort for reactogenicity.

5.9.5. Derived and transformed data

Demography

For a given subject and a given demographic variable, missing measurement was not replaced. Therefore, analysis of demography excluded subjects with missing measurements.

Efficacy

An episode of GE was classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain was identified in a stool sample collected during the episode. GE episode without stool sample/result available was not considered in the analysis as a RV GE episode.

To assess the intensity of RV GE using the 20-point Vesikari scale:

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting) were calculated by counting the number of days with presence (>0) of looser than normal stool (vomiting). Missing value at a specific day was considered as absence of looser than normal stool (vomiting) at that day.
- The maximum number of looser than normal stool (vomiting or fever) was defined as the maximum value observed from the number of looser than normal stool (vomiting or fever) recorded daily during the GE episode.
- Since the dehydration was not recorded in the eCRF, the following rule was applied**:** a subject that had a GE episode was considered as being dehydrated between 1 to 5% if this subject received oral rehydration; a subject was considered as being dehydrated $\geq$ 6 % if the subject was hospitalized and/or received intravenous (IV) rehydration.

To assess the intensity of RV GE using the 24-point Clark scale:

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting, fever or behavioral symptoms) was calculated by counting the number of days with presence (> 0) of looser than normal stool (vomiting, fever or behavioral symptoms). Missing value at a specific day was considered as absence of looser than normal stool (vomiting, fever or behavioral symptoms) at that day.
- The maximum number of looser than normal stool (vomiting or fever) was defined as the maximum value observed from the number of looser than normal stool (vomiting or fever) recorded daily during the GE episode.

Immunogenicity

The cut-off values of all antibodies were defined by the laboratory before the analysis and as described in Section 5.6.1.

A seronegative subject was a subject whose concentration/titer was below the cut-off value.

A seropositive subject was a subject whose concentration/titer was greater than or equal to the cut-off value.

Seroprotection was defined as antibody concentration/titer greater than or equal to the seroprotection level.

Seroconversion was defined as the appearance of antibodies (i.e. concentration/titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.

The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis of immunogenicity excluded subjects with missing or non-evaluable measurements.

Reactogenicity

For a given dose, subjects with no symptoms (solicited or unsolicited) documented were considered as subjects without symptoms (solicited or unsolicited).

5.9.6. Analysis of drop-outs, demographics and intercurrent vaccinations

The distributions of subjects enrolled by country and among the study centers in each country were tabulated by group.

The numbers of subjects who dropped out at Visit 5 were tabulated by group according to the reason for drop-out.

The median, mean, range and standard deviation of age at Dose 1 and Dose 2 of HRV vaccine or placebo (in weeks), and at Visit 5 or at last contact if Visit 5 was not performed (in months) were calculated by group for each analyzed cohort (pooled countries) and for each country for the total vaccinated cohort. The racial and gender composition was also presented. The median, mean and standard deviation of height in cm and weight in kg at Visit 1 were also tabulated. The BMI (Body Mass Index) at Visit 1 was also calculated as weight (in kg) / height^2 (in meters).

Feeding criteria on the day of each study vaccination were tabulated by group for pooled countries and for each country for the ATP cohort for efficacy and the ATP cohort for immunogenicity.

The percentage of subjects who completed the two-dose study vaccination course before the RV epidemic season was tabulated for the ATP cohort for efficacy.

Epidemiological data in terms of the number of siblings per subject and the attendance to day care center at each visit were tabulated for pooled countries and for each country for the total vaccinated cohort.

A summary of childhood vaccinations co-administered with each dose of HRV vaccine or placebo was presented by country for the total vaccinated cohort, for the total vaccinated cohort for the reactogenicity and immunogenicity subset in Finland, the ATP cohort for efficacy and the ATP cohort for immunogenicity.

Intercurrent vaccinations from birth until 30 days post Dose 2 of HRV vaccine or placebo were tabulated by group per country for the total vaccinated cohort and the total vaccinated cohort for the immunogenicity and reactogenicity subset in Finland.

The number of days between Dose 2 and Dose 3 of childhood routine vaccinations were summarized by group per country for ATP cohort for immunogenicity and the total vaccinated cohort for the immunogenicity and reactogenicity subset.

The number of days between Dose 2/Dose 3 of childhood routine vaccinations and post-vaccination blood sampling were summarized by group per country for ATP cohort for immunogenicity and the total vaccinated cohort for the immunogenicity and reactogenicity subset.

The number of childhood vaccination doses received from Visit 1 up to 21 days before post Dose 2/ post Dose 3 blood sample were tabulated by country for the ATP cohort for immunogenicity and the total vaccinated cohort for the immunogenicity and reactogenicity subset.

5.9.7. Analysis of efficacy

The first efficacy period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at Visit 5. Analysis of efficacy during the first efficacy period was performed on the ATP cohort for efficacy. Analysis of efficacy from the first dose onwards was performed on the total vaccinated cohort.

Only GE episodes in which wild-type RV (i.e. other than the vaccine strain) was identified in a stool specimen were included in the efficacy analysis.

A global overview of the number of GE episodes of any etiology (RV or not) and RV GE episodes reported during the first efficacy period was provided for pooled countries.

Number of GE episodes with no available stool results during the first efficacy period was provided for pooled countries.

Number of GE episodes and RV GE episodes reported during the first efficacy period, by severity using the Vesikari scale was presented for pooled countries.

Characteristics of GE episodes reported during the first efficacy period were tabulated for pooled countries.

A summary of RV GE episodes reported during the first efficacy period by isolated G and P types was provided for pooled countries and for each country.

Seasonal distributions of the GE episodes and of RV GE episodes reported during the first efficacy period were displayed for pooled countries and for each country.

The duration of the first efficacy period (in years) was tabulated by group for pooled countries.

For the ATP cohort for efficacy (primary analysis), VE estimates were calculated, with their 95% CI against:

- Any RV GE during the period starting from 2 weeks after Dose 2 up to Visit 5
- Severe RV GE during the period starting from 2 weeks after Dose 2 up to Visit 5
- Any and severe RV GE caused by G1 type during the period starting from 2 weeks after Dose 2 up to Visit 5
- Any and severe RV GE caused by non-G1 types during the period starting from 2 weeks after Dose 2 up to Visit 5
- Hospitalization due to RV GE during the period starting from 2 weeks after Dose 2 up to Visit 5
- RV GE requiring medical attention during the period starting from 2 weeks after Dose 2 up to Visit 5

The VE was defined as the percent reduction in the frequency of the relevant endpoint in vaccinated subjects compared with those subjects who received placebo. This was calculated as follows:

VE = vaccine efficacy = 1- RR = 1 – (ARV/ARU)

Where:

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 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.

RR = relative risk = ARV/ARU

The 95% CIs for VE were derived using a conditional to cases approach. See Appendix 2I for mathematical details about the computation of the 95% CI for VE.

In order to assess VE from Dose 1 onwards, VE against all endpoints evaluated in the ATP analysis was calculated for the period from Dose 1 up to Visit 5. Also, VE against any and severe RV GE were calculated for the period from Dose 1 to before Dose 2 and

from Dose 1 up to Day 14 after Dose 2. These analyses were performed only on the total vaccinated cohort.

For the period starting from 2 weeks after Dose 2 up to Visit 5, exploratory VE was also calculated against each isolated RV type, severe RV GE with Clark score >16, by serological status for IgA antibody concentration at Visit 3, by feeding criteria, all cause GE, by country, all cause severe GE and hospitalization due to all cause GE.

For each of the above-mentioned efficacy endpoint, the percentages of subjects reporting at least one episode were compared between groups using two-sided Fisher's exact test (significance level of α=0.05).

To check the robustness with respect to the statistical analysis, VE against any RV GE, any RV GE due to G1 type and any RV GE due to non-G1 types during the first efficacy follow-up period and their 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 any RV GE, any RV GE due to G1 type and any RV GE due to non-G1 types. The time was censored at the last contact in the first efficacy follow-up period.

5.9.8. Analysis of immunogenicity

Immunogenicity was evaluated in subjects who were part of the immunogenicity and reactogenicity subset.

Anti-rotavirus IgA antibody response

Anti-rotavirus IgA antibody response was calculated on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort for immunogenicity and reactogenicity subset.

GMCs and seropositivity/seroconversion rates for anti-rotavirus IgA antibodies were calculated with their 95% CIs for each group at Visit 1, Visit 3 and Visit 4 (Spain only). These calculations were performed for pooled countries and for each country.

Anti-rotavirus IgA antibody GMCs and their 95% CI were also calculated on subjects seropositive for anti-rotavirus IgA antibody for pooled countries and for each country.

A Reverse Cumulative Distribution Curve (RCC) for anti-rotavirus IgA antibody concentration at Visit 3 was generated for pooled countries

The two-sided asymptotic standardized 95% CI for the difference (HRV minus Placebo) in seroconversion rates to anti-rotavirus IgA antibody at Visit 3 was calculated for pooled countries.

Analysis of anti-rotavirus IgA antibody response was also presented by feeding criteria.

Immunogenicity of co-administered childhood vaccinations

Post Dose 3 immunogenicity in Czech Republic, France, Germany and Spain, and post Dose 2 immunogenicity in Finland, Italy and Spain were calculated on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort for immunogenicity and reactogenicity subset.

The interim analyses on post Dose 3 immunogenicity of childhood vaccinations for Finland and Italy were performed on the total vaccinated cohort for the immunogenicity and reactogenicity subset.

GMCs/GMTs and seropositivity/seroprotection rates for antibodies to co-administered antigens were calculated with their 95% CIs for each group at post Dose 3 of childhood vaccinations per country.

Similar calculations were also performed at post Dose 2 of childhood vaccinations for Finland, Italy and Spain.

Antibody concentrations or titers post Dose 2/Dose 3 of childhood vaccinations were displayed by country using RCCs.

The two-sided asymptotic standardized 95% CI for difference (Placebo minus HRV) in post Dose 2/Dose 3 seropositivity/seroprotection rates was calculated for each co-administered antigen by country.

The 95% CI for the ratio of post Dose 2/Dose 3 GMCs/GMTs (Placebo over HRV) was computed for each co-administered antigen by country (using a one-way ANOVA model on the logarithm10 transformation of the titers).

Post-hoc descriptive analysis was performed to evaluate the post Dose 3 immunogenicity of co-administered childhood vaccinations specifically for Center [redacted] and for the German cohort excluding Center [redacted] Only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample were included in these analyses.

5.9.9. Analysis of reactogenicity and safety

The analyses of reactogenicity and safety planned numerous group comparisons through P-value computation. The P-values were used as an aid to highlight potential imbalances worth further attention (significance level of alpha = 0.05) and care was to be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment, and the rate of false signals could be considerably large due to the number of comparisons. When a potential imbalance between groups was noted, individual AE cases were reviewed by a sponsor physician and conclusions were based on clinical judgement.

Reactogenicity

Analysis of reactogenicity was performed on the total vaccinated cohort for immunogenicity and reactogenicity subset.

The number of doses administered, the number of symptom sheets transcribed for general symptoms and the compliance for general symptoms was tabulated for pooled countries and for each country. Compliance was defined as the number of general symptom sheets completed divided by the number of doses administered for a specified vaccination (dose) and group.

The percentage, with exact 95% CI, of doses followed by any solicited or unsolicited symptoms during the solicited 8-day follow-up period after vaccination was tabulated per dose and overall and by group. The percentage, with exact 95% CI, of subjects with any solicited or unsolicited symptoms was also tabulated per group. Similar tabulations were done for grade 3 symptoms (solicited or unsolicited) and for symptoms (solicited or unsolicited) with relationship assessed as related to the vaccine. These analyses were generated for pooled countries.

The percentage of doses, with exact 95 % CI, reporting each individual solicited general symptom, symptoms assessed as related to the vaccine and symptoms grade 3 in intensity, during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated for each group, after each dose. An overall dose analysis and the percentage, with exact 95 % CI, of subjects reporting each of the individual solicited general symptoms was also tabulated. These analyses were generated for pooled countries and for each country.

Prevalence of diarrhea, vomiting and fever by day during the solicited follow-up period was described graphically for pooled countries. Prevalence was the percentage of subjects who reported the event at a certain (fixed) time point among doses administered.

The differences between the HRV vaccine group and the Placebo group were explored for pooled countries using the two-sided Fisher's exact test (significant level of alpha = 0.05) for the endpoints mentioned below:

- the percentage of subjects reporting each solicited symptom including those rated as grade 3 in intensity and those assessed as related to vaccination during the 8-day solicited follow-up period, after any HRV or placebo doses.

Safety

Analysis of safety was performed on the total vaccinated cohort.

As an introduction to the safety results, an overview of the number of vaccine doses received in each group and overall was provided for pooled countries and for each country.

The verbatim of unsolicited symptoms obtained from the investigators were reviewed by a GSK Biologicals' physician and the signs, symptoms and diagnoses were coded to the most appropriate lowest level term according to according to the MedDRA which was then linked to the primary System Organ Class (SOC) and Preferred Terms (PT) for analysis.

The percentage of subjects with unsolicited symptoms reporting within 31 days were summarized by group, for pooled countries, according to the MedDRA SOC and PTs and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05). Similar tables were generated for grade 3 symptoms and for symptoms assessed as related to vaccination.

In addition, the percentages of doses with unsolicited symptoms reporting within 31 days were summarized by group, for pooled countries, according to the MedDRA SOC and PTs. Similar tables were generated for grade 3 symptoms and for symptoms assessed as related to vaccination.

The percentage of subjects who reported an SAE/IS from Dose 1 of HRV vaccine or placebo up to Visit 5 were computed by group, for pooled countries, and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05).

The number and percentage of subjects who started taking concomitant medication during the 8-day solicited follow-up period were tabulated by type of medication for pooled countries.

Withdrawals until Visit 5 due to AEs or SAEs were described.

5.9.10. Interim analyses

In order to obtain early data in relation to other studies, a planned interim analysis on reactogenicity and immunogenicity was performed on subjects from the Czech Republic and Finland who were part of the immunogenicity and reactogenicity subset (data lock point: 29 June 2005). This analysis presented a descriptive summary of reactogenicity data on solicited and unsolicited symptoms**,** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccinations co-administered with each study vaccine dose. Summaries by group were generated by S-Clinica, the analysis center supporting the IDMC, in order to maintain the sponsor blinded with respect to individual treatment data. Summaries across groups were generated within GSK Biologicals. No study report was written for the interim results.

In order to obtain early data on immunogenicity post Dose 3 of childhood vaccinations for Finland, an interim analyses on the total vaccinated cohort for the immunogenicity and reactogenicity subset for Finland (data lock point: 15 February 2006) and Italy (data lock point: 28 February 2006) were performed at GSK Biologicals. The descriptive results of the interim analyses are included in this study report.

5.10. Changes in the conduct of the study or planned analyses

5.10.1. Protocol amendments

The protocol was amended on 07 June 2005 while the study was ongoing. Measurement of anti-PSC antibody concentrations by ELISA for subset from Spain was added. Details of the reactogenicity interim analysis were described. SAE contact information, study contact information, sponsor information were updated.

5.10.2. Other Changes

Analyses were performed as planned in the protocol and in the reporting and analysis plan finalized on 03 November 2005, except for the following change.

- Analysis of VE in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season was not performed as 90.2% of subjects were vaccinated during the RV epidemic season.
- An interim analysis was performed on the total vaccinated cohort for the immunogenicity and reactogenicity subset in Finland and Italy to calculate GMCs/GMTs and seropositivity/seroprotection rates for antibodies to co-administered antigens at post Dose 3 of childhood vaccinations.
- Post-hoc descriptive analysis was performed to evaluate the post Dose 3 immunogenicity of co-administered childhood vaccinations specifically for Center [redacted] and for the German cohort excluding Center [redacted] Only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample were included in these analyses.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject was enrolled in this study on 08 September 2004 and the last subject was enrolled on 01 February 2005. The last Visit 5 took place on 07 September 2005. The data lock point for post Dose 3 immunogenicity of childhood vaccinations was 15 February 2006 for Finland and 28 February 2006 for Italy.

6.2. Subject eligibility and attrition from study

6.2.1. Number and distribution of subjects

Table 15 presents the number of subjects enrolled per group for the total vaccinated cohort (pooled countries and per country). Supplement 1 presents the number of subjects enrolled at each center by group for the total vaccinated cohort.

A total of 3994 subjects were enrolled and received at least one dose of HRV or placebo, with 72.4% of the total enrolment in Finland. France and Italy did not reach the planned enrolment of 300 subjects each.

Table 15 Number of subjects enrolled in each country, by group – Total vaccinated cohort

	HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	199	7.5	100	7.4	299	7.5
Finland	1918	72.5	972	72.1	2890	72.4
France	95	3.6	51	3.8	146	3.7
Germany	190	7.2	99	7.3	289	7.2
Italy	15	0.6	10	0.7	25	0.6
Spain	229	8.7	116	8.6	345	8.6

N = number of subjects enrolled in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects enrolled in a given country

Of the 2890 subjects enrolled in Finland, 300 subjects were part of the immunogenicity and reactogenicity subset. For all other countries, all enrolled subjects were part of this subset. In total, 1404 subjects were part of the immunogenicity and reactogenicity subset.

6.2.2. Withdrawal at Visit 5

Of the 3994 subjects who received at least one dose of HRV or placebo, Visit 5 was completed by 3944 subjects (98.7%). Table 16 summarizes the subjects vaccinated, completed and dropped-out and reasons for drop-out.

Table 16 Counts of subjects vaccinated, completed and dropped-out with reason for drop-out at Visit 5 – Total vaccinated cohort

	Group		
	HRV	**Placebo**	**Total**
Number of subjects enrolled and vaccinated	2646	1348	3994
Number of subjects who completed Visit 5	2613	1331	3944
Number of dropped-out subjects at Visit 5	33	17	50
Reasons for drop out :			
SAE	0	4	4
Non-serious AE	7	2	9
Protocol violation	0	0	0
Consent withdrawal (not due to an AE)	21	4	25
Migrated/moved from study area	2	5	7
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	3	2	5
Others	0	0	0

Enrolled and vaccinated = number of subjects who where enrolled in the study and received at least one dose of HRV or placebo
Completed = number of subjects who completed study Visit 5
Dropped-out = number of subjects who did not come to study Visit 5

Four subjects from the Placebo group dropped-out at Visit 5 due to SAEs. Refer to Section 9.5 for details.

Nine subjects (7 from the HRV vaccine group and 2 from the Placebo group) dropped-out at Visit 5 due to non-serious AEs. Refer to Section 9.6 for details.

6.2.3. Protocol deviations

6.2.3.1. Protocol deviations leading to exclusion of subjects from an analysis

The number of subjects enrolled and eligible for inclusion in the ATP cohort for efficacy for the first efficacy follow-up period and reasons for elimination are summarized in

Table 17. Subjects could be attributed more than one elimination code; in the table subjects are listed on the basis of the lowest elimination code.

ATP cohort for efficacy

Of the 3994 subjects included in the total vaccinated cohort, 120 subjects were eliminated from the ATP cohort for efficacy for the following reasons:

- Ten subjects had received intercurrent vaccines forbidden in the protocol (elimination code 1040). Of these, seven subjects had received Bacille Calmette-Guérin (BCG) vaccination within 2 weeks of HRV vaccine or placebo dose. Three subjects, from Spain received Prevenar within 2 weeks of HRV vaccine or placebo dose (co-administration of Prevenar was not planned in Spain).
- The randomization code was broken for one subject who reported IS on Day 8 after Dose 2 (elimination code 1060). Refer to Section 9.5.2 for details on the IS case.
- [redacted]
- Fifty-two subjects who were part of the of the immunogenicity and reactogenicity subset were eliminated because of initially positive or unknown status for serum anti-rotavirus IgA antibodies at Visit 1 (elimination code 1500).
- Thirty-five subjects did not receive Dose 2 of HRV vaccine or placebo (elimination code 3010).
- Three subjects had a last contact before efficacy follow-up period began at two weeks after Dose 2 (elimination code 3020).
- GE stool samples collected between Dose 1 till 2 weeks after Dose 2 from 10 subjects were positive for RV other than the vaccine strain (elimination code 3030).

Thus, 3874 subjects (2572 in the HRV vaccine group and 1302 in the Placebo group) were included in the ATP cohort for efficacy for the first efficacy follow-up period.

Table 17 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for efficacy with reasons for exclusion – Pooled countries

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	**3994**						
Total vaccinated cohort	**3994**		**100**	**2646**		**1348**	
Administration of intercurrent vaccine(s) forbidden in the protocol (code 1040)	10	10		7	7	3	3
Randomization code broken (code 1060)	1	1		1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	9	9		6	6	3	3
Initially positive or unknown status for serum anti-rotavirus IgA antibodies on the day of dose 1 (code 1500)	52	52		31	31	21	21
At least one study vaccine dose not administered (code 3010)	35	35		25	25	10	10
Subjects not entered into the surveillance period of the first efficacy follow-up period (code 3020)	3	3		2	2	1	1
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response (code 3030)	10	10		2	2	8	8
ATP cohort for efficacy - first efficacy follow-up period	**3874**		**97.0**	**2572**		**1302**	

For cohorts:

n = number of subjects in the cohort.

% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort.

For reasons of exclusion:

Subjects may have more than one elimination code assigned.

Therefore for each reason for elimination, (s) is provided where:

n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number.

s = number of subjects with the elimination code assigned.

The ATP cohort for analysis of efficacy during the first efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one thousand or three thousand with the exception of code 1035.

The number of subjects enrolled and eligible for inclusion in the ATP cohort for reactogenicity and for ATP cohort for immunogenicity and reasons for elimination are summarized in Table 18. Subjects could be attributed more than one elimination code; in the table subjects are listed on the basis of the lowest elimination code.

Total vaccinated cohort

The total vaccinated cohort consisted of 3994 subjects (2646 subjects in the HRV vaccine group and 1348 subjects in the Placebo group) with at least one study vaccine administration documented. The total vaccinated cohort was used for the analysis of safety.

Total vaccinated cohort for the immunogenicity and reactogenicity subset

Of the 3994 subjects in the total vaccinated cohort, 1404 subjects (914 subjects in the HRV vaccine group and 490 subjects in the Placebo group) who were planned to provide reactogenicity data were part of the total vaccinated cohort for the immunogenicity and reactogenicity subset. 2590 subjects not planned to be part of the immunogenicity and reactogenicity subset were assigned elimination code 1035.

The total vaccinated cohort for the immunogenicity and reactogenicity subset was used for the analysis of reactogenicity and secondary analysis of immunogenicity.

ATP cohort for reactogenicity

Of the 1404 subjects in the total vaccinated cohort for the immunogenicity and reactogenicity subset, 61 subjects were eliminated from the ATP cohort for reactogenicity for the following reasons:

- Three subjects, from Spain received Prevenar within 2 weeks of HRV vaccine or placebo dose (co-administration of Prevenar was not planned in Spain) (elimination code 1040).
- The randomization code was broken for one subject who reported IS on Day 8 after Dose 2 (elimination code 1060). Refer to Section 9.5.2 for details on the IS case.
- [redacted]
- Fifty-two subjects were eliminated because of initially positive or unknown status for serum anti-rotavirus IgA antibodies on the day of Dose 1 of HRV vaccine or placebo (elimination code 1500).

Thus, 1343 subjects (875 subjects in the HRV vaccine group and 468 subjects in the Placebo group) were included in the ATP cohort for reactogenicity.

Reactogenicity analysis on the ATP cohort for reactogenicity was not performed since 4.3% of subjects from the total vaccinated cohort for the immunogenicity and reactogenicity subset were excluded from the ATP cohort.

ATP cohort for immunogenicity

Of the 1343 subjects included in the ATP cohort for reactogenicity, 127 were excluded from ATP cohort for immunogenicity for the following reasons:

- Ten subjects were eliminated because of protocol violation related to inclusion/exclusion criteria (elimination code 2010).
- Twelve subjects were eliminated because GE stool samples collected between Visit 1 and post-vaccination blood sampling visit to measure anti-rotavirus IgA antibodies were positive for RV other than the vaccine strain (elimination code 2060).

- Fourteen subjects were eliminated due to non-compliance with vaccination schedule since they received Dose 2 of HRV vaccine or placebo outside of the required interval between vaccinations (see Table 4) (elimination code 2080).
- Thirty-four subjects were eliminated due to non-compliance with blood sampling schedule (elimination code 2090).
- Fifty-seven subjects were eliminated because post-vaccination serology results were not available mainly because of invalid results or blood sample not collected (elimination code 2100).

Thus, 1216 subjects (794 in the HRV vaccine group and 422 in the Placebo group) were included in the ATP cohort for immunogenicity.

Table 18 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for reactogenicity and from the ATP cohort for immunogenicity with reasons for exclusion – Pooled countries

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	**3994**						
Total vaccinated cohort	**3994**		**100**	**2646**		**1348**	
Subjects for whom solicited symptoms were not to be collected and who were not planned to be bled for all blood sampling visits (code 1035)	2590	2590		1732	1732	858	858
Total vaccinated cohort for the immunogenicity and reactogenicity subset	**1404**		**35.2**	**914**		**490**	
Administration of intercurrent vaccine(s) forbidden in the protocol (code 1040)	3	10		3	7	0	3
Randomization code broken (code 1060)	1	1		1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	5	9		4	6	1	3
Initially positive or unknown status for serum anti-rotavirus IgA antibodies on the day of dose 1 (code 1500)	52	52		31	31	21	21
ATP cohort for reactogenicity	**1343**		**33.6**	**875**		**468**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	10	13		5	6	5	7
Concomitant infection by rotavirus other than vaccine strain which may influence immune response (code 2060)	12	12		3	3	9	9
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	14	36		8	21	6	15
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	34	38		20	22	14	16
Essential serological data missing (code 2100)	57	64		45	50	12	14
ATP cohort for immunogenicity	**1216**		**30.4**	**794**		**422**	

For cohorts:

n = number of subjects in the cohort.

% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort.

For reasons of exclusion:

Subjects may have more than one elimination code assigned.

Therefore for each reason for elimination, n (s) is provided where:

n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number.

s = number of subjects with the elimination code assigned.

The ATP cohort for reactogenicity includes all vaccinated subjects with no elimination codes beginning with one thousand.

The ATP cohort for immunogenicity includes all vaccinated subjects with no elimination codes beginning with one thousand or two thousand.

6.2.3.2. Protocol deviations not leading to exclusion of subjects from an analysis

Subjects, who completed Visit 5 outside the planned time period of mid-June to end-July 2005, were not eliminated from ATP cohort for efficacy for this reason.

6.3. Demographic characteristics

6.3.1. ATP cohort for efficacy

Demographic characteristics of the ATP cohort for efficacy (pooled countries) are summarized in Table 19.

For the pooled countries, the demographic profile of the two groups was similar in terms of the median age at each dose, gender distribution and race. The median age at Dose 1 was 12.0 weeks and at Dose 2 was 20.0 weeks. The median age at Visit 5 or at last contact if Visit 5 was not performed was 11 months. The study population was predominantly White/Caucasian. There were more males than females in both groups.

Table 19 Summary of demographic characteristics – Pooled countries – ATP cohort for efficacy

		HRV N = 2572		Placebo N = 1302		Total N = 3874	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	11.5	-	11.5	-	11.5	-
	SD	1.77	-	1.78	-	1.77	-
	Minimum	5	-	6	-	5	-
	Median	12.0	-	12.0	-	12.0	-
	Maximum	18	-	16	-	18	-
Age at Dose 2 (weeks)	**Mean**	19.7	-	19.7	-	19.7	-
	SD	2.68	-	2.72	-	2.69	-
	Minimum	10	-	10	-	10	-
	Median	20.0	-	20.0	-	20.0	-
	Maximum	30	-	27	-	30	-
Age at visit 5 or at last contact if visit 5 not performed (Months)	**Mean**	10.3	-	10.4	-	10.3	-
	SD	1.45	-	1.44	-	1.44	-
	Minimum	3	-	5	-	3	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	13	-	13	-	13	-
Gender	**Female**	1194	46.4	639	49.1	1833	47.3
	Male	1378	53.6	663	50.9	2041	52.7
Race	**African heritage**	6	0.2	5	0.4	11	0.3
	White/Caucasian	2531	98.4	1278	98.2	3809	98.3
	Arabic/north African	9	0.3	3	0.2	12	0.3
	East/south east Asian	1	0.0	1	0.1	2	0.1
	South Asian	4	0.2	1	0.1	5	0.1
	American Hispanic	12	0.5	5	0.4	17	0.4
	Japanese	0	0.0	0	0.0	0	0.0
	Other	9	0.3	9	0.7	18	0.5
Height (cm)	**Mean**	60.5	-	60.5	-	60.5	-
	SD	2.91	-	2.92	-	2.92	-
	Median	61.0	-	61.0	-	61.0	-
	Unknown	2	-	3	-	5	-
Weight (kg)	**Mean**	6.0	-	6.0	-	6.0	-
	SD	0.86	-	0.84	-	0.85	-
	Median	6.0	-	6.0	-	6.0	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	**Mean**	16.4	-	16.3	-	16.4	-
	SD	1.52	-	1.54	-	1.52	-
	Median	16.3	-	16.3	-	16.3	-
	Unknown	2	-	3	-	5	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter SD = standard deviation

A summary of feeding criteria at Dose 1 and Dose 2 of HRV vaccine or placebo is presented in Supplement 2 for pooled countries and for each country. For pooled countries, 66.0% of subjects were breast-fed at the time of both doses of HRV vaccine or placebo, 12.6% of subjects were breast-fed at the time of one dose of HRV vaccine or placebo and 21.4% of subjects were not breast-fed at any dose of HRV vaccine or

placebo. The percentages of subjects who were breast-fed or not breast-fed were similar between the groups.

Percentage of subjects who completed the two-dose study vaccination course before the RV epidemic season is presented in Supplement 3 for pooled countries and for each country. For pooled countries, 90.2% of subjects were vaccinated during the RV epidemic season. The study had a secondary objective to evalaute VE in subjects who completed the two-dose vaccination course before the RV epidemic season versus those who were vaccinated during the RV epidemic season. This objective was not evaluated as the majority of subjects were vaccinated during the early part of the RV epidemic season.

6.3.2. Total vaccinated cohort

Supplement 4 presents the demographic characteristics of the total vaccinated cohort (pooled countries). For the pooled countries, the demographic profile (median age at each dose, distribution of male and female subjects and race) of the two groups was similar. The median age at Dose 1 was 12.0 weeks and at Dose 2 was 20.0 weeks.

Supplement 5 to Supplement 10 presents the demographic characteristics of the total vaccinated cohort for each country.

A summary of data on day care attendance and number of siblings is presented in Supplement 11 for pooled countries and for each country. For pooled countries, 99.6% of subjects were not at a day care center at the time of Visit 1. At Visit 5, 94.2% of subjects were still not going to a day care center and 4.6% of subjects were at a day care center.

6.3.3. Total vaccinated cohort for the immunogenicity and reactogenicity subset

Supplement 12 presents the demographic characteristics of the total vaccinated cohort for the immunogenicity and reactogenicity subset (pooled countries). The demographic profile (median age at each dose, distribution of male and female subjects and race) of the two groups was similar. The median age at Dose 1 was 11.0 weeks and at Dose 2 was 17.0 weeks.

6.3.4. ATP cohort for immunogenicity

Supplement 13 presents the demographic characteristics of the ATP cohort for immunogenicity (pooled countries). The demographic profile (median age at each dose, distribution of male and female subjects and race) of the two groups was similar. The median age at Dose 1 was 11.0 weeks and at Dose 2 was 17.0 weeks.

A summary of feeding criteria at Dose 1 and Dose 2 of HRV or placebo is presented in Supplement 14 for pooled countries and for each country. For pooled countries, 59.1% of subjects were breast-fed at the time of Dose 1 and Dose 2 of HRV vaccine or placebo, 14.7% of subjects were breast-fed at the time of one dose of HRV vaccine or placebo and 26.2% of subjects were not breast-fed at any dose of HRV vaccine or placebo. The

percentages of subjects who were breast-fed or not breast-fed were similar between the groups.

6.4. Concomitant and intercurrent vaccinations

Total vaccinated cohort

A summary of vaccinations co-administered with Dose 1 and Dose 2 of HRV vaccine or placebo for each country is presented in Supplement 15 and Supplement 16 respectively.

- In the total vaccinated cohort, the majority of subjects in each country received the nationally recommended childhood vaccinations (Infanrix Hexa in all countries, Infanrix Polio Hib in France at Dose 2, Prevenar in France and Germany and Meningitec in Spain) on the same day as each dose of HRV vaccine or placebo. Overall, at least 98.5% of subjects received childhood vaccinations with Dose 1 of HRV vaccine or placebo, and at least 99.0% of subjects received childhood vaccinations with Dose 2 of HRV vaccine or placebo.

A summary of vaccinations other than HRV vaccine or placebo administered from birth until 30 days post Dose 2, excluding vaccinations given on the day of HRV vaccine or placebo doses, (intercurrent vaccinations) for each country are presented in Supplement 17, Supplement 18 and Supplement 19.

ATP cohort for efficacy

A summary of vaccinations co-administered with Dose 1 and Dose 2 of HRV vaccine or placebo for each country is presented in Supplement 20 and Supplement 21 respectively. Co-administration of childhood vaccinations for the ATP cohort for efficacy was similar to the total vaccinated cohort.

ATP cohort for immunogenicity

A summary of vaccinations co-administered with Dose 1 and Dose 2 of HRV vaccine or placebo is presented in Supplement 22 and Supplement 23 respectively. Co-administration of childhood vaccinations for the ATP cohort for immunogenicity was similar to the total vaccinated cohort.

Supplement 24 to Supplement 27 present the number of days between the 2^{nd} and the 3^{rd} dose of childhood vaccinations and between the 2^{nd} or 3^{rd} dose of childhood vaccinations and the post-vaccination blood sampling for each country. The intervals between the different timepoints were similar for the two groups in each country.

The total numbers of childhood vaccination doses received from Visit 1 up to 21 days before post Dose 2/ post Dose 3 blood sampling are presented in Supplement 28 to Supplement 39 for each country. An interval of minimum 21 days between Dose 2/Dose 3 and post-vaccination blood sampling was needed to elicit adequate immune response (see Table 4).

- From Visit 1 up to 21 days before post Dose 3 blood sampling, three doses of Infanrix Hexa were received by 81.3% subjects in Czech Republic, 74.9% in Germany and 100% in Spain. From Visit 1 up to 21 days before post Dose 3 blood sampling in France, two doses of Infanrix Hexa were received by 98.4% subjects and 100% received one dose of Infanrix Polio Hib.
- The interval between Dose 2 of Infanrix Hexa and the post-vaccination blood sampling was at least 21 days for 100% each for Finland and Italy.
- From Visit 1 up to 21 days before post Dose 3 blood sampling, three doses of Meningitec were received by 100% subjects in Spain.
- From Visit 1 up to 21 days before post Dose 3 blood sampling, three doses of Prevenar were received by 99.2% in France and 74.1% in Germany.

Total vaccinated cohort for the immunogenicity and reactogenicity subset

A summary of vaccinations co-administered with Dose 1 and Dose 2 of HRV vaccine or placebo for Finland is presented in Supplement 40 and Supplement 41 respectively.

A summary of vaccinations other than HRV vaccine or placebo administered from birth until 30 days post Dose 2, excluding vaccinations given on the day of HRV vaccine or placebo doses, (intercurrent vaccinations) for Finland is presented in Supplement 42, Supplement 43 and Supplement 44.

Supplement 45 to Supplement 48 present the number of days between the 2nd and the 3rd dose of childhood vaccinations and between the 2nd or 3rd dose of childhood vaccinations and the post-vaccination blood sampling for each country. The intervals between the different timepoints were similar for the two groups in each country.

The total numbers of childhood vaccination doses received from Visit 1 up to 21 days before post Dose 2/ post Dose 3 blood sampling are presented in Supplement 49 to Supplement 60 for each country.

7. VACCINE EFFICACY RESULTS DURING THE FIRST EFFICACY PERIOD

7.1. Data sets analyzed

Analysis of efficacy was performed on the ATP cohort (primary analysis) for VE during the first efficacy period that started 2 weeks after Dose 2 and ended at Visit 5, and the total vaccinated cohort for VE from Dose 1 onwards. See Section 5.9.4 for definition of cohorts identified for analyses and Section 6.2.3.1 for eligibility for analysis.

Only GE episodes in which wild-type RV (i.e. other than the vaccine strain) was identified in a stool specimen were to be included in the efficacy analysis.

From Dose 1 of HRV vaccine or placebo up to Visit 5, RV vaccine strain was detected in the stools of five GE episodes. All of these episodes were reported during the period from

Dose 1 up to 2 weeks post Dose 2 of HRV vaccine or placebo. The G1P8 vaccine strain cases were excluded from the efficacy analysis; the GE episode with mixed wild-type RV was included in the efficacy analysis from Dose 1 up to 2 weeks post Dose 2. There were no cases of GE with vaccine strain RV detected during the first efficacy period.

Table 20 presents a summary of GE episodes with vaccine strain isolated.

Table 20 Vaccine strain RV GE episodes from Dose 1 up to Visit 5 - Total vaccinated cohort

Country	Previous dose	Onset (days)	Medical attention	Vesikari score	Clark score	Isolated G and P types
Finland	1	2	No	3	2	G1P8 vaccine strain
Finland	1	4	No	2	2	G1P8 vaccine strain
Finland	1	6	Medical contact without visit	3	3	G1P8 vaccine strain
Finland	1	6	No	2	2	G1P8 vaccine strain
Finland	2	6	No	5	3	G1P8 vaccine strain and G9P8 wild type

7.2. ATP cohort for efficacy

The ATP cohort for efficacy included 3874 subjects (2572 subjects in the HRV vaccine group and 1302 subjects in the Placebo group).

7.2.1. Characterization of GE episodes

Table 21 presents the percentage of subjects who reported GE episodes and RV GE episodes during the first efficacy period (from two weeks after Dose 2 of HRV vaccine or placebo up to Visit 5). Table 22 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.

During the first efficacy period (mean duration: 6 months in each group, Supplement 61), 1060 GE episodes of any cause were reported by 898 subjects. Of these, 647 GE episodes were reported in 559 subjects in the HRV vaccine group and 413 GE episodes were reported in 339 subjects from the Placebo group.

Supplement 62 presents characteristics of GE episodes reported during the first efficacy period. The duration of vomiting and the rate of hospitalization for all cause GE were lower in the HRV vaccine group compared the Placebo group.

Supplement 63 presents the percentage of GE episodes reported during the first efficacy follow-up period with no available stool analysis results. Stool analysis results were available for 593/647 (91.7%) GE episodes in the HRV vaccine group and for 369/413 (89.3%) GE episodes in the Placebo group. No stool analysis results were available for 54 samples from the HRV vaccine group and 44 samples from the Placebo group due to insufficient quantity of stool samples collected, stool sample not tested or stools not collected.

Of all the GE episodes tested, RV was detected in 24 GE episodes from the HRV vaccine group and 94 GE episodes from the Placebo group. No subject in either group had more than one episode of RV GE during the first efficacy period (Table 21).

When the GE episodes were scored using the 20-point Vesikari scale, 20.8% RV GE episodes in the HRV vaccine group and 63.8% RV GE episodes in the Placebo group were rated as severe (Vesikari score ≥ 11 points) (Table 22). Supplement 64 presents the distribution of Vesikari score for the RV GE episodes.

Table 21 Percentage of subjects who reported GE episodes and RV GE episodes from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

Event	Total number of episode reported	HRV N = 2572 n	%	Placebo N = 1302 n	%
GE	**1**	483	18.8	277	21.3
	2	66	2.6	53	4.1
	3	8	0.3	6	0.5
	4	2	0.1	3	0.2
	Any	559	21.7	339	26.0
RV GE	**1**	24	0.9	94	7.2
	Any	24	0.9	94	7.2

N = number of subjects included in each group
n/% = number/percentage of subjects with the specified total number of episode reported
Any = number and percentage of subjects with at least one specified episode reported

Table 22 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5, by severity using the 20-point Vesikari scale - ATP cohort for efficacy

Event	Severity using Vesikari scale	HRV n	%	Placebo n	%
GE	**Mild (1-6)**	302	46.7	157	38.0
	Moderate (7-10)	224	34.6	124	30.0
	Severe (≥11)	120	18.5	132	32.0
	Unknown	1	0.2	0	0.0
	Any	647	100	413	100
RV GE	**Mild (1-6)**	8	33.3	11	11.7
	Moderate (7-10)	11	45.8	23	24.5
	Severe (≥11)	5	20.8	60	63.8
	Any	24	100	94	100

n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported
Any = any specified symptom reported, regardless of Vesikari severity scale

Table 23 presents the number of RV GE episodes by G and P types. Supplement 65 presents the percentage of subjects with RV GE episodes by G and P types. Supplement 66 presents the number of severe RV GE episodes by G and P types in each country.

The G types isolated during the first efficacy period were G1 wild-type, G2, G3, G4 and G9. Genotype P8 wild-type was associated with G1, G3, G4 and G9 types and genotype P4 was associated with the G2 type. Both G1P8 wild-type and G4P8 RV were isolated

from one episode in the Placebo group. The P genotype was not typable for one episode from the Placebo group in which the G2 type was isolated. From the rates in the placebo group, G1P8 wild-type was the most prevalent type circulating during the first efficacy period, followed by the G9P8 type.

Table 23 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5, by G and P types - ATP cohort for efficacy

	HRV N'= 24		Placebo N'= 94	
Type	**n**	**%**	**N**	**%**
G1wt and P8wt	4	16.7	45	47.9
G2 and P4	3	12.5	3	3.2
G3 and P8wt	1	4.2	5	5.3
G4 and P8wt	3	12.5	12	12.8
G9 and P8wt	13	54.2	27	28.7
G1w and G4 and P8wt	0	0.0	1	1.1
G2 and unknown P type	0	0.0	1	1.1

N' = number of RV GE episodes reported
n/% = number/percentage of RV GE episodes reported in each group, by G and P types
wt = wild type

Supplement 67 presents characteristics of RV GE episodes reported during the first efficacy period. Supplement 68, Supplement 69 and Supplement 70 present the characteristics of RV GE episodes by isolated RV types. The duration of vomiting and diarrhea and rate of hospitalization for RV GE episodes were lower in the HRV vaccine group as compared to the Placebo group.

Supplement 71 to Supplement 83 present seasonal distribution of GE episodes and RV GE episodes (except for Italy where no RV GE cases were reported) for pooled countries and per country.

7.2.2. Vaccine efficacy against any RV GE (primary endpoint)

Table 24 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild-type RV during the first efficacy period.

Significantly fewer subjects in the HRV vaccine group reported any RV GE caused by the circulating wild-type RV compared to the Placebo group (two-sided Fisher's exact P-value < 0.001). VE against any RV GE was 87.1% (95% CI: 79.6%; 92.1%). The primary efficacy objective of the study was reached since the lower limit of the 95% CI for the vaccine efficacy was above 50% (criteria specified for fulfilling the primary efficacy objective).

Table 24 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	24	0.9	0.6	1.4	87.1	79.6	92.1	<0.001
Placebo	1302	94	7.2	5.9	8.8				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

Using the Cox proportional-hazard model, VE against any RV GE caused by the circulating wild-type RV during the first efficacy period was 87.4% (95% CI: 80.3%; 91.9%). Results of analysis using the Cox proportional-hazard model are available on file at GSK Biologicals, Rixensart.

7.2.3. Vaccine efficacy against severe RV GE

Table 25 presents the efficacy of the HRV vaccine against severe RV GE (Vesikari score ≥11 points) caused by the circulating wild-type RV.

Significantly fewer subjects in the HRV vaccine group reported severe RV GE caused by the circulating wild-type RV compared to the Placebo group (P-value < 0.001). VE against severe RV GE was 95.8% (95% CI: 89.6%; 98.7%).

Table 25 Percentage of subjects reporting severe (Vesikari score ≥11 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	5	0.2	0.1	0.5	95.8	89.6	98.7	<0.001
Placebo	1302	60	4.6	3.5	5.9				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 84 and Supplement 85 present efficacy of the HRV vaccine against RV GE with a score ≥ a specific value on the Vesikari scale. The point estimates of VE appear to increase with higher Vesikari score, and reached 100% against RV GE with a score ≥ 17 points on the Vesikari scale.

7.2.4. Vaccine efficacy against circulating RV types

7.2.4.1. Vaccine efficacy against any RV GE by RV type

Table 26 presents the efficacy of the HRV vaccine against any RV GE, by isolated RV types. If more than one wild-type RV was detected in specimens from a RV GE episode, then this episode was counted in each of the detected RV type category in Table 26.

Significantly fewer subjects in the HRV vaccine group reported any RV GE episodes caused by G1 wild-type in the HRV vaccine group compared with the Placebo group (P-value < 0.001). VE against any RV GE caused by G1 wild-type was 95.6% (95% CI: 87.9%; 98.8%).

When considering all isolated non-G1 types (G2, G3, G4 and G9), significantly fewer subjects in the HRV vaccine group reported any RV GE compared with the Placebo group (P-value < 0.001). VE against any RV GE caused by non-G1 types was 79.3% (95% CI: 64.6%; 88.4%).

Type specific VE against any RV GE episodes caused by non-G1 RV types was also observed.

- Any RV GE episodes caused by G2 type were reported by 0.1% of subjects in the HRV vaccine group and 0.3% of subjects in the Placebo group. The difference between groups did not reach statistical significance (P-value = 0.234). VE against any RV GE caused by G2 type was 62.0% (95% CI: -124.4%; 94.4%).
- Significantly fewer subjects in the HRV vaccine group reported any RV GE episodes caused by G3 type compared with the Placebo group (P-value = 0.018). VE against any RV GE caused by G3 type was 89.9% (95% CI: 9.5%; 99.8%).
- Significantly fewer subjects in the HRV vaccine group reported any RV GE episodes caused by G4 type compared with the Placebo group (P-value < 0.001). VE against any RV GE caused by G4 type was 88.3% (95% CI: 57.5%; 97.9%).
- Significantly fewer subjects in the HRV vaccine group reported any RV GE episodes caused by G9 type compared with the Placebo group (P-value < 0.001). VE against any RV GE caused by G9 type was 75.6% (95% CI: 51.1%; 88.5%).

Table 26 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5, by RV type - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2572	4	0.2	0.0	0.4	95.6	87.9	98.8	<0.001
Placebo	1302	46†	3.5	2.6	4.7				
Pooled Non G1 (G2, G3, G4, G9)									
HRV	2572	20	0.8	0.5	1.2	79.3	64.6	88.4	<0.001
Placebo	1302	49	3.8	2.8	4.9				
G2									
HRV	2572	3	0.1	0.0	0.3	62.0	-124.4	94.4	0.234
Placebo	1302	4	0.3	0.1	0.8				
G3									
HRV	2572	1	0.0	0.0	0.2	89.9	9.5	99.8	0.018
Placebo	1302	5	0.4	0.1	0.9				
G4									
HRV	2572	3	0.1	0.0	0.3	88.3	57.5	97.9	<0.001
Placebo	1302	13†	1.0	0.5	1.7				
G9									
HRV	2572	13	0.5	0.3	0.9	75.6	51.1	88.5	<0.001
Placebo	1302	27	2.1	1.4	3.0				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one specified RV GE episode in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)
† One subject from the Placebo group counted in G1 and G4 categories since both RV types were isolated

Using the Cox proportional-hazard model, VE against any RV GE caused by G1 wild-type was 95.6% (95% CI: 87.9%; 98.4%) and VE against any RV GE caused by non-G1 types was 79.5% (95% CI: 65.5%; 87.8%). Results of analysis using the Cox proportional-hazard model are available on file at GSK Biologicals, Rixensart.

7.2.4.2. Vaccine efficacy against severe RV GE by RV type

Table 27 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11 points) RV GE, by isolated RV types. If more than one wild-type RV was detected in specimens from a severe RV GE episode, then this episode was counted in each of the detected RV type category in Table 27.

Significantly fewer subjects in the HRV vaccine group reported severe RV GE episodes caused by G1 wild-type in the HRV vaccine group compared with the Placebo group (P-value < 0.001). VE against severe RV GE caused by G1 wild-type was 96.4% (95% CI: 85.7%; 99.6%).

When considering all isolated non-G1 types (G2, G3, G4 and G9), significantly fewer subjects in the HRV vaccine group reported severe RV GE compared with the Placebo group (P-value < 0.001). VE against severe RV GE caused by non-G1 types was 95.4% (95% CI: 85.3%; 99.1%).

Type specific VE against severe RV GE episodes (Vesikari score ≥11 points) caused by non-G1 RV types was observed.

- Severe RV GE episodes caused by G2 type was reported by 0% of subjects in the HRV vaccine group and 0.2% of subjects in the Placebo group. The difference between groups did not reach statistical significance (P-value = 0.263). VE against severe RV GE caused by G2 type was 74.7% (95% CI: -386.2%; 99.6%).
- Significantly fewer subjects in the HRV vaccine group reported severe RV GE episodes caused by G3 type compared with the Placebo group (P-value = 0.004). VE against severe RV GE caused by G3 type was 100% (95% CI: 44.8%; 100%).
- Significantly fewer subjects in the HRV vaccine group reported severe RV GE episodes caused by G4 type compared with the Placebo group (P-value < 0.001). VE against severe RV GE caused by G4 type was 100% (95% CI: 64.9%; 100%).
- Significantly fewer subjects in the HRV vaccine group reported severe RV GE episodes caused by G9 type compared with the Placebo group (P-value < 0.001). VE against severe RV GE caused by G9 type was 94.7% (95% CI: 77.9%; 99.4%).

Table 27 Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5, by RV type - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2572	2	0.1	0.0	0.3	96.4	85.7	99.6	<0.001
Placebo	1302	28†	2.2	1.4	3.1				
Pooled Non G1 (G2, G3, G4, G9)									
HRV	2572	3	0.1	0.0	0.3	95.4	85.3	99.1	<0.001
Placebo	1302	33	2.5	1.8	3.5				
G2									
HRV	2572	1	0.0	0.0	0.2	74.7	-386.2	99.6	0.263
Placebo	1302	2	0.2	0.0	0.6				
G3									
HRV	2572	0	0.0	0.0	0.1	100	44.8	100	0.004
Placebo	1302	5	0.4	0.1	0.9				
G4									
HRV	2572	0	0.0	0.0	0.1	100	64.9	100	<0.001
Placebo	1302	7†	0.5	0.2	1.1				
G9									
HRV	2572	2	0.1	0.0	0.3	94.7	77.9	99.4	<0.001
Placebo	1302	19	1.5	0.9	2.3				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one specified severe RV GE episode in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)
† One subject from the Placebo group counted in G1 and G4 categories since both RV types were isolated

7.2.5. Vaccine efficacy against hospitalization due to RV GE

Table 28 presents the efficacy of the HRV vaccine against hospitalization due to RV GE caused by the circulating wild-type RV.

No subject in the HRV vaccine group was hospitalized for RV GE, while 12 subjects in the Placebo group required hospitalized for RV GE caused by the circulating wild-type RV. A significant reduction in hospitalization for RV GE was observed in the HRV vaccine group compared to the Placebo group (P-value < 0.001), resulting in VE of 100% (95% CI: 81.8%; 100%).

Table 28 Percentage of subjects hospitalized due to RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	0	0.0	0.0	0.1	100	81.8	100	<0.001
Placebo	1302	12	0.9	0.5	1.6				

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized due to RV GE episode caused by the circulating wild-type RV
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

7.2.6. Vaccine efficacy against RV GE requiring medical attention

Table 29 presents the efficacy of the HRV vaccine against RV GE episodes caused by the circulating wild-type RV requiring medical attention (defined in the protocol as medical provider contact, advice, visit; emergency room contact or visit or hospitalization).

Significantly fewer subjects in the HRV vaccine group required medical attention for RV GE caused by the circulating wild-type RV compared to the Placebo group (P-value < 0.001). VE against RV GE episodes requiring medical attention was 91.8% (95% CI: 84.0%; 96.3%).

Table 29 Percentage of subjects reporting RV GE requiring medical attention and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	10	0.4	0.2	0.7	91.8	84.0	96.3	<0.001
Placebo	1302	62	4.8	3.7	6.1				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with medical attention in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

7.2.7. Vaccine efficacy against all cause GE

Table 30 presents the efficacy of the HRV vaccine against all cause GE episodes.

All cause GE was reported by significantly fewer subjects in the HRV vaccine group compared to the Placebo group (P-value = 0.003). VE against all cause GE was 16.5% (95% CI: 4.2%; 27.2%).

Significantly fewer subjects in the HRV vaccine group reported all cause GE rated as severe (Vesikari score ≥11 points) or requiring hospitalization compared to the Placebo group (P-value < 0.001 for each comparison). VE against all cause GE rated as severe

was 52.3% (95% CI: 38.0%; 63.3%). VE against all cause GE requiring hospitalization was 74.7% (95% CI: 45.5%; 88.9%).

Table 30 Percentage of subjects reporting all cause GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
All-cause GE									
HRV	2572	559	21.7	20.2	23.4	16.5	4.2	27.2	0.003
Placebo	1302	339	26.0	23.7	28.5				
All cause severe GE (Vesikari score ≥11 points)									
HRV	2572	116	4.5	3.7	5.4	52.3	38.0	63.3	<0.001
Placebo	1302	123	9.4	7.9	11.2				
All cause GE requiring hospitalization									
HRV	2572	11	0.4	0.2	0.8	74.7	45.5	88.9	<0.001
Placebo	1302	22	1.7	1.1	2.5				

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one specified GE episode regardless of any cause in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

7.2.8. Vaccine efficacy against RV GE by serological status for IgA antibody concentration at Visit 3

Supplement 86 and Supplement 87 present VE against any RV GE and severe RV GE (Vesikari score ≥11 points) caused by the circulating wild-type RV according to the serological status for anti-rotavirus IgA antibodies at Visit 3.

It should be noted that anti-rotavirus IgA antibody results were available for a subset of the efficacy cohort. Among the IgA seropositive subjects, any RV GE was reported by significantly fewer subjects in the HRV vaccine group compared to the Placebo group (P-value = 0.010), resulting in VE of 95.6% (95% CI: 39.8%; 99.7%); severe RV GE was reported in 0.1% subjects in the HRV vaccine group and 0% in the Placebo group. The results in seronegative subjects show a possible trend towards some degree of protection despite absence of serum IgA. VE in subjects whose IgA seropositivity status was not known was consistent with overall efficacy results. Overall, since IgA response was evaluated only in a subset of subjects, it was difficult to draw a conclusion on correlation between seroconversion rate and VE.

7.2.9. Vaccine efficacy against RV GE by feeding criteria

Supplement 88 and Supplement 89 present VE against any RV GE and severe RV GE (Vesikari score ≥11 points) caused by the circulating wild-type RV by feeding criteria.

The VE estimates were consistent between children who were breast-fed at the time of at least one dose of HRV vaccine and children who were not breast-fed at any dose.

7.2.9.1. Vaccine efficacy against RV GE scored using the Clark scale

Supplement 90 presents a summary of intensity of GE and RV GE episodes using the Clark scale. Supplement 91 presents the distribution of Clark score for the RV GE episodes. Supplement 92 to Supplement 95 present the characteristics of RV GE episodes using the Clark scale. Supplement 96 present the characteristics of GE episodes using the Clark scale.

Supplement 97 presents the efficacy of the HRV vaccine against severe RV GE according to the Clark scale. Supplement 98 presents the efficacy of the HRV vaccine against severe RV GE according to the Clark scale, by RV type. Supplement 99 and Supplement 100 present efficacy of the HRV vaccine against RV GE with a score ≥ a specific value on the Clarke scale.

When the RV GE episodes were scored using the Clark scale, 8.3% RV GE episodes in the HRV vaccine group and 16.0% RV GE episodes in the Placebo group were rated as severe (Clark score >16 points).

Comparing the Vesikari and Clark scales, there were more severe RV GE when using Vesikari scale (score ≥11 points) (5 in HRV vaccine group and 60 in the Placebo group) as compared to the Clark scale (score >16 points) (2 in the HRV vaccine group and 15 in the Placebo group). Despite these differences in the two scales, the observed VE against severe RV GE was similar.

7.2.10. Vaccine efficacy by country

Supplement 101 to Supplement 106 present VE by country.

Due to the smaller sample size in some countries (and consequently fewer RV GE episodes), the difference between groups did not reach statistical significance.

Significantly fewer subjects in the HRV vaccine group reported any RV GE caused by the circulating wild-type RV compared with the Placebo group in Finland where a sufficiently large sample size was enrolled (N=2849 in the ATP cohort for efficacy). In Finland, VE was 88.6% (95% CI: 81.0%; 93.4%) against any RV GE and 96.4% (95% CI: 90.2%; 99.1%) against severe RV GE, which is consistent with results for overall efficacy.

7.3. Total vaccinated cohort

The total vaccinated cohort was used to evaluate VE against RV GE occurring from Dose 1 onwards.

7.3.1. Vaccine efficacy against RV GE during the period from Dose 1 to Visit 5

Supplement 107 to Supplement 140 present results during the period from Dose 1 to Visit 5.

Efficacy estimates for the period from Dose 1 up to Visit 5 (mean duration: 8 months in each study group) were consistent with results of the primary analysis on the ATP cohort for efficacy for the period from 2 weeks after dose 2 to Visit 5. The results indicated that HRV vaccine was protective starting from Dose 1 onwards.

During the period from Dose 1 to Visit 5, significantly fewer subjects in the HRV vaccine group reported any RV GE and severe RV GE (Vesikari score ≥11 points) caused by the circulating wild-type RV compared to the Placebo group (P-value < 0.001). VE was 87.3% (95% CI: 80.3%; 92.0%) against any RV GE and 96.0% (95% CI: 90.2%; 98.8%) against severe RV GE.

7.3.2. Vaccine efficacy against RV GE during the period from Dose 1 to 2 weeks post Dose 2

Supplement 141 to Supplement 150 present results during the period from Dose 1 to 14 days post Dose 2.

During the period from Dose 1 to14 days post Dose 2 (mean duration: 2.4 months in each study group), significantly fewer subjects in the HRV vaccine group reported any RV GE caused by the circulating wild-type RV compared to the Placebo group (P-value = 0.004). VE against any RV GE was 87.3% (95% CI: 36.2%; 98.7%).

7.3.3. Vaccine efficacy against RV GE during the period from Dose 1 to before Dose 2

Supplement 151 to Supplement 160 present results during the period from Dose 1 to before Dose 2.

During the period from Dose 1 to before Dose 2 (mean duration: 1.9 months in each study group), significantly fewer subjects in the HRV vaccine group reported any RV GE caused by the circulating wild-type RV compared to the Placebo group (P-value = 0.019). VE against any RV GE was 89.8% (95% CI: 8.9%; 99.8%).

7.4. Efficacy conclusions

- Two oral doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccinations were highly effective compared to the placebo in protecting infants against any RV GE caused by the circulating wild-type RV during the first efficacy period. VE against any RV GE was 87.1% (95% CI: 79.6%; 92.1%). The primary objective of this study was met.
- Two oral doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccinations were highly effective during the first efficacy period compared to the placebo in protecting infants against:
  - Severe RV GE caused by the circulating wild-type RV; VE 95.8% (95% CI: 89.6%; 98.7%)
  - Any RV GE caused by G1 wild-type RV; VE 95.6% (95% CI: 87.9%; 98.8%)

- Severe RV GE caused by G1 wild-type RVs; VE 96.4% (95% CI: 85.7%; 99.6%)
- Any RV GE caused by non-G1 RV types; VE 79.3% (95% CI: 64.6%; 88.4%)
- Severe RV GE caused by non-G1 RV types; VE 95.4% (95% CI: 85.3%; 99.1%)
- Hospitalization due to RV GE caused by the circulating wild-type RV; VE 100% (95% CI: 81.8%; 100%)
- RV GE episodes caused by the circulating wild-type RV requiring medical attention; 91.8% (95% CI: 84.0%; 96.3%)

- Already after the first dose, GSK Biologicals' HRV vaccine was protective against any and severe RV GE caused by the circulating wild-type RV. VE against any RV GE was 89.8% (95% CI: 8.9%; 99.8%) during the period from Dose 1 to before Dose 2. VE estimates for the period from Dose 1 until Visit 5 were consistent with estimates for the first efficacy period.

8. IMMUNOGENICITY RESULTS

8.1. Data sets analyzed

Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and the total vaccinated cohort for the immunogenicity and reactogenicity. See Section 5.9.4 for the definition of the cohorts identified for analyses and Section 6.2.3.1 for eligibility for analyses.

8.2. ATP cohort for immunogenicity

The ATP cohort for immunogenicity consisted of 1216 subjects (794 subjects in the HRV vaccine group and 422 subjects in the Placebo group).

8.2.1. Anti-rotavirus IgA antibody response

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each timepoint are presented in Table 31. Supplement 161 presents RCCs of anti-rotavirus IgA antibody concentrations at Visit 3.

Anti-rotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%) was observed in the HRV vaccine group at one to two months after Dose 2 of HRV vaccine co-administered with childhood vaccinations. 6.7% (95% CI: 4.5%; 9.5%) subjects in the Placebo group were seropositive for anti-rotavirus IgA antibodies at one to two months after Dose 2 of placebo.

Immunogenicity of HRV vaccine was good in each country. The anti-rotavirus IgA seroconversion rates at one to two months after Dose 2 of HRV vaccine ranged between 82.1% (95% CI: 75.1%; 87.7%) and 94.6% (95% CI: 90.0%; 97.5%) among countries.

The observed IgA seroconversion rate in Finland seems to be higher than in the other countries. As this study was not designed to examine differences in IgA response between countries, valid conclusion can not be drawn. The differences between countries are likely due to different schedules used in different countries.

Table 31 Seroconversion rates and GMCs for anti-rotavirus IgA antibodies - ATP cohort for immunogenicity

				≥ 20 U/ml				GMC (U/ml)		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
All	HRV	PRE	794	0	0.0	0.0	0.5	< 20	-	-
		PII(M3-M4)	787	681	**86.5**	**83.9**	**88.8**	197.2	175.2	222.0
		PII(M5)	184	152	82.6	76.3	87.8	113.3	90.8	141.5
	Placebo	PRE	422	0	0.0	0.0	0.9	< 20	-	-
		PII(M3-M4)	420	28	6.7	4.5	9.5	< 20	-	-
		PII(M5)	90	14	15.6	8.8	24.7	< 20	-	-
Czech Republic	HRV	PRE	182	0	0.0	0.0	2.0	< 20	-	-
		PII(M3-M4)	182	154	84.6	78.5	89.5	152.5	118.9	195.4
	Placebo	PRE	90	0	0.0	0.0	4.0	< 20	-	-
		PII(M3-M4)	90	2	2.2	0.3	7.8	< 20	-	-
Finland	HRV	PRE	167	0	0.0	0.0	2.2	< 20	-	-
		PII(M3-M4)	167	158	94.6	90.0	97.5	412.2	325.9	521.2
	Placebo	PRE	105	0	0.0	0.0	3.5	< 20	-	-
		PII(M3-M4)	105	3	2.9	0.6	8.1	< 20	-	-
France	HRV	PRE	83	0	0.0	0.0	4.3	< 20	-	-
		PII(M3-M4)	83	70	84.3	74.7	91.4	181.8	126.4	261.6
	Placebo	PRE	43	0	0.0	0.0	8.2	< 20	-	-
		PII(M3-M4)	43	6	14.0	5.3	27.9	< 20	-	-
Germany	HRV	PRE	156	0	0.0	0.0	2.3	< 20	-	-
		PII(M3-M4)	156	128	82.1	75.1	87.7	166.0	126.0	218.9
	Placebo	PRE	84	0	0.0	0.0	4.3	< 20	-	-
		PII(M3-M4)	84	5	6.0	2.0	13.3	< 20	-	-
Italy	HRV	PRE	13	0	0.0	0.0	24.7	< 20	-	-
		PII(M3-M4)	13	12	92.3	64.0	99.8	205.1	80.5	522.7
	Placebo	PRE	9	0	0.0	0.0	33.6	< 20	-	-
		PII(M3-M4)	9	1	11.1	0.3	48.2	< 20	-	-
Spain	HRV	PRE	193	0	0.0	0.0	1.9	< 20	-	-
		PII(M3-M4)	186	159	85.5	79.6	90.2	156.3	123.4	198.0
		PII(M5)	184	152	82.6	76.3	87.8	113.3	90.8	141.5
	Placebo	PRE	91	0	0.0	0.0	4.0	< 20	-	-
		PII(M3-M4)	89	11	12.4	6.3	21.0	< 20	-	-
		PII(M5)	90	14	15.6	8.8	24.7	< 20	-	-

HRV vaccine or placebo was administered at 3, 4 months of age in Czech Republic; 2, 3 months of age in France and Germany; 2, 4 months of age in Spain; 3, 5 months in Finland and Italy
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Table 32 presents the anti-rotavirus IgA antibody GMCs calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at Visit 3 and Visit 4 (tested only in Spain).

Table 32 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies after two doses of HRV vaccine or placebo - ATP cohort for immunogenicity

				GMC (U/ml)		
					95% CI	
Country	Group	Timing	N	value	LL	UL
All	HRV	PII(M3-M4)	681	**313.7**	**284.2**	**346.1**
		PII(M5)	152	189.0	157.3	226.9
	Placebo	PII(M3-M4)	28	290.9	159.3	531.2
		PII(M5)	14	172.9	82.7	361.5
Czech Republic	HRV	PII(M3-M4)	154	250.2	202.0	309.9
	Placebo	PII(M3-M4)	2	840.9	78.9	8961.3
Finland	HRV	PII(M3-M4)	158	509.4	416.1	623.7
	Placebo	PII(M3-M4)	3	149.0	1.5	14845.5
France	HRV	PII(M3-M4)	70	311.6	234.5	414.0
	Placebo	PII(M3-M4)	6	259.1	28.9	2325.3
Germany	HRV	PII(M3-M4)	128	307.0	246.1	383.1
	Placebo	PII(M3-M4)	5	801.7	151.3	4247.8
Italy	HRV	PII(M3-M4)	12	263.8	114.8	606.3
	Placebo	PII(M3-M4)	1	57.0	-	-
Spain	HRV	PII(M3-M4)	159	249.3	204.3	304.2
		PII(M5)	152	189.0	157.3	226.9
	Placebo	PII(M3-M4)	11	224.3	93.6	537.3
		PII(M5)	14	172.9	82.7	361.5

N = number of subjects who seroconverted for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Supplement 162 presents the difference in seroconversion rate at one to two months after Dose 2 of HRV vaccine or placebo between the HRV vaccine group and Placebo group. The lower limit of the two-sided asymptotic standardized 95% CI for the difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody at Visit 3 between the HRV vaccine group and (minus) the Placebo group was 76.2% indicating that the seroconverison rate was significantly higher in the HRV vaccine group as compared to the Placebo group.

Supplement 163 and Supplement 164 present anti-rotavirus IgA antibody response by feeding criteria for pooled countries. Breast-feeding did not appear to have an impact on anti-rotavirus IgA response as shown by similar IgA seroconversion rate/GMCs in both groups.

8.2.2. Post Dose 3 immunogenicity of childhood vaccinations in Czech Republic, France, Germany and Spain

The immunogenicity of the childhood vaccinations was assessed after the full 3-dose primary vaccination course in Czech Republic, France, Germany and Spain and results for each antigen are presented in Section 8.2.2.1 to Section 8.2.2.8.

The two first doses of Infanrix Hexa were to be co-administered with each HRV vaccine or placebo dose in each country; Infanrix Polio Hib was to be co-administered with the

2nd dose of HRV vaccine or placebo in France. Meningitec was to be co-administered in Spain, and Prevenar was to be co-administered in France and Germany. Subjects were to receive the 3rd dose of childhood vaccination series as per the recommended schedule in their country (without HRV).

Three doses of childhood vaccinations were received from Visit 1 up to 21 days before post Dose 3 blood sampling by the majority of subjects (81.3% to 100%) in Czech Republic, France, and Spain; 74% of subjects in Germany received three doses of childhood vaccinations up to 21 days before post Dose 3 blood sampling (See Supplement 28 to Supplement 39).

8.2.2.1. Anti-meningococcal serogroup C antibodies

SBA-MenC antibodies

The percentages of subjects with SBA-MenC antibody titers ≥ 1/8 and ≥ 1/128 and GMTs post Dose 3 of Meningitec are shown in Table 33. Supplement 165 presents RCC for SBA-MenC antibody titers post Dose 3 of Meningitec.

At Post Dose 3 of Meningitec, 100% of subjects from both groups in Spain had SBA-MenC antibody titers ≥ 1:8. 98.4% of subjects in the HRV vaccine group and 100% in the Placebo group had SBA-MenC antibody titers ≥ 1:128. The post Dose 3 SBA-MenC antibody seropositivity rates and GMTs were similar between the two groups.

Table 33 Seropositivity rates and GMTs for anti-SBA-MenC antibodies post Dose 3 of Meningitec - ATP cohort for immunogenicity

				≥ 1:8 dilution				≥ 1:128 dilution				GMT		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Spain	HRV	PIII(M3-M5)	184	184	100	98.0	100	181	98.4	95.3	99.7	1455.4	1240.2	1707.9
	Placebo	PIII(M3-M5)	90	90	100	96.0	100	90	100	96.0	100	1769.1	1374.3	2277.5

Meningitec was administered at 2, 4 and 6 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 4)

Anti-PSC antibodies

The percentages of subjects with anti-PSC antibody concentrations ≥ 0.3 µg/ml and ≥ 2.0 µg/ml and GMCs post Dose 3 of Meningitec are shown in Table 34. Supplement 166 presents RCC for anti-PSC antibody concentrations post Dose 3 of Meningitec.

At Post Dose 3 of Meningitec, 100% of subjects from both groups in Spain had anti-PSC antibody concentrations ≥ 0.3 µg/ml. 97.9% of subjects in the HRV vaccine group and 96.7% of subjects in the Placebo group had anti-PSC antibody concentrations ≥ 2.0 µg/ml. The post Dose 3 anti-PSC antibody seropositivity rates and GMCs were similar between the two groups.

Table 34 Seropositivity rates and GMCs for anti-PSC antibodies post Dose 3 of Meningitec - ATP cohort for immunogenicity

				≥ 0.3 µg/ml				≥ 2.0 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Spain	**HRV**	**PIII(M3-M5)**	187	187	100	98.0	100	183	97.9	94.6	99.4	7.63	6.81	8.55
	Placebo	**PIII(M3-M5)**	91	91	100	96.0	100	88	96.7	90.7	99.3	8.76	7.56	10.15

Meningitec was administered at 2, 4 and 6 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post -Dose 3 of childhood vaccinations (Visit 4)

8.2.2.2. Antibody response to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F

Seropositivity rates and GMCs for antibodies to pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 of Prevenar are shown in Table 35. Supplement 167 to Supplement 180 present RCC for antibodies to each of the seven pneumococcal serotypes post Dose 3 of Prevenar.

Post Dose 3 seropositivity rates and GMCs for antibodies to pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F were similar between the two groups and results were consistent between France and Germany.

Table 35 Seropositivity rates and GMCs for antibodies to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 of Prevenar - ATP cohort for immunogenicity

					≥ 0.05 µg/ml				≥ 0.2 µg/ml				GMC (µg/ml)		
							95% CI				95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Pneumonia serotype 4	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	83	100	95.7	100	2.40	2.02	2.85
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	43	100	91.8	100	2.39	2.02	2.83
	Germany	HRV	PIII(M3-M5)	155	155	100	97.6	100	155	100	97.6	100	3.17	2.80	3.59
		Placebo	PIII(M3-M5)	84	84	100	95.7	100	84	100	95.7	100	3.11	2.56	3.78
Pneumonia serotype 6B	France	HRV	PIII(M3-M5)	83	80	96.4	89.8	99.2	69	83.1	73.3	90.5	0.79	0.59	1.07
		Placebo	PIII(M3-M5)	43	42	97.7	87.7	99.9	38	88.4	74.9	96.1	0.65	0.46	0.93
	Germany	HRV	PIII(M3-M5)	155	138	89.0	83.0	93.5	107	69.0	61.1	76.2	0.48	0.37	0.63
		Placebo	PIII(M3-M5)	84	77	91.7	83.6	96.6	59	70.2	59.3	79.7	0.49	0.35	0.70
Pneumonia serotype 9V	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	83	100	95.7	100	2.42	2.06	2.84
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	43	100	91.8	100	2.39	2.00	2.86
	Germany	HRV	PIII(M3-M5)	155	155	100	97.6	100	154	99.4	96.5	100	2.94	2.57	3.36
		Placebo	PIII(M3-M5)	84	84	100	95.7	100	84	100	95.7	100	2.65	2.13	3.29
Pneumonia serotype 14	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	83	100	95.7	100	4.68	3.75	5.84
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	43	100	91.8	100	5.29	4.22	6.63
	Germany	HRV	PIII(M3-M5)	155	155	100	97.6	100	154	99.4	96.5	100	4.59	3.93	5.37
		Placebo	PIII(M3-M5)	84	84	100	95.7	100	83	98.8	93.5	100	3.89	2.99	5.08
Pneumonia serotype 18C	France	HRV	PIII(M3-M5)	83	81	97.6	91.6	99.7	80	96.4	89.8	99.2	2.47	1.92	3.18
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	43	100	91.8	100	2.56	2.03	3.24
	Germany	HRV	PIII(M3-M5)	155	155	100	97.6	100	154	99.4	96.5	100	3.40	2.89	4.01
		Placebo	PIII(M3-M5)	84	84	100	95.7	100	82	97.6	91.7	99.7	3.31	2.62	4.19
Pneumonia serotype 19F	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	81	97.6	91.6	99.7	2.85	2.30	3.52
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	42	97.7	87.7	99.9	2.75	2.05	3.69
	Germany	HRV	PIII(M3-M5)	155	155	100	97.6	100	154	99.4	96.5	100	3.62	3.06	4.27
		Placebo	PIII(M3-M5)	84	84	100	95.7	100	84	100	95.7	100	3.51	2.87	4.29
Pneumonia serotype 23F	France	HRV	PIII(M3-M5)	83	82	98.8	93.5	100	76	91.6	83.4	96.5	1.25	0.95	1.65
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	41	95.3	84.2	99.4	1.35	1.01	1.80
	Germany	HRV	PIII(M3-M5)	155	147	94.8	90.1	97.7	137	88.4	82.3	93.0	1.31	1.03	1.68
		Placebo	PIII(M3-M5)	84	80	95.2	88.3	98.7	71	84.5	75.0	91.5	1.21	0.84	1.75

Prevenar was administered at 2, 3 and 4 months of age
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3)

8.2.2.3. Antibody response to diphtheria toxoid and tetanus toxoid

Anti-diphtheria and anti-tetanus antibody GMCs and seroprotection rates post Dose 3 of childhood vaccinations are presented in Table 36. Supplement 181 to Supplement 184 present RCC for post Dose 3 anti-diphtheria antibody concentrations. Supplement 185 to Supplement 188 present RCC for post Dose 3 anti-tetanus antibody concentrations.

In each country, post Dose 3 anti-diphtheria and anti-tetanus antibody GMCs and seroprotection rates were similar in both groups.

Table 36 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccinations – ATP cohort for immunogenicity

					≥ 0.1 IU/ml				GMC (IU/ml)		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	Czech Republic	HRV	PIII(M3-M5)	182	182	100	98.0	100	2.321	2.097	2.569
		Placebo	PIII(M3-M5)	89	89	100	95.9	100	2.694	2.292	3.165
	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	1.168	0.963	1.417
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	1.118	0.838	1.490
	Germany	HRV	PIII(M3-M5)	155	148	95.5	90.9	98.2	1.389	1.140	1.694
		Placebo	PIII(M3-M5)	84	83	98.8	93.5	100	1.350	1.058	1.723
	Spain	HRV	PIII(M3-M5)	188	188	100	98.1	100	6.653	6.077	7.284
		Placebo	PIII(M3-M5)	91	91	100	96.0	100	6.830	5.865	7.953
Anti-tetanus	Czech Republic	HRV	PIII(M3-M5)	182	182	100	98.0	100	1.918	1.690	2.177
		Placebo	PIII(M3-M5)	90	90	100	96.0	100	1.789	1.499	2.136
	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	1.353	1.126	1.627
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	1.384	1.112	1.723
	Germany	HRV	PIII(M3-M5)	155	152	98.1	94.4	99.6	1.094	0.919	1.302
		Placebo	PIII(M3-M5)	84	84	100	95.7	100	1.150	0.924	1.430
	Spain	HRV	PIII(M3-M5)	188	187	99.5	97.1	100	1.665	1.469	1.888
		Placebo	PIII(M3-M5)	90	90	100	96.0	100	1.669	1.408	1.978

Infanrix Hexa was administered at: 3, 4, 5 months of age in Czech Republic; 2, 3, 4 months of age in France (Infanrix Polio Hib given at Dose 2) and Germany; 2, 4, 6 months of age in Spain
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3 for Czech Republic, France and Germany; Visit 4 for Spain)

8.2.2.4. Antibody response to PT, FHA and PRN

Anti-PT, anti-FHA and anti-PRN antibody GMCs and seropositivity rates post Dose 3 of childhood vaccinations are presented in Table 37. Supplement 189 to Supplement 200 present post Dose 3 RCCs for anti- PT, anti-FHA and anti-PRN antibody concentrations.

In each country, post Dose 3 anti-PT, anti-FHA and anti-PRN antibody GMCs and seropositivity rates were similar in both groups.

Table 37 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 3 of childhood vaccinations - ATP cohort for immunogenicity

					≥ 5 EL.U/ml				GMC (EL.U/ml)		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Czech Republic	HRV	PIII(M3-M5)	181	180	99.4	97.0	100	55.6	50.6	61.0
		Placebo	PIII(M3-M5)	90	90	100	96.0	100	53.4	46.5	61.3
	France	HRV	PIII(M3-M5)	83	83	100	95.7	100	42.1	37.2	47.8
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	46.3	39.3	54.5
	Germany	HRV	PIII(M3-M5)	153	140	91.5	85.9	95.4	30.2	25.7	35.5
		Placebo	PIII(M3-M5)	82	77	93.9	86.3	98.0	28.4	23.2	34.7
	Spain	HRV	PIII(M3-M5)	188	187	99.5	97.1	100	42.9	39.0	47.2
		Placebo	PIII(M3-M5)	91	91	100	96.0	100	45.1	40.3	50.5
Anti-FHA	Czech Republic	HRV	PIII(M3-M5)	182	182	100	98.0	100	215.8	196.4	237.2
		Placebo	PIII(M3-M5)	90	90	100	96.0	100	214.8	188.2	245.1
	France	HRV	PIII(M3-M5)	82	82	100	95.6	100	176.2	153.4	202.4
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	180.3	152.5	213.0
	Germany	HRV	PIII(M3-M5)	155	152	98.1	94.4	99.6	110.3	90.3	134.8
		Placebo	PIII(M3-M5)	84	82	97.6	91.7	99.7	97.5	74.7	127.3
	Spain	HRV	PIII(M3-M5)	188	188	100	98.1	100	159.2	144.6	175.3
		Placebo	PIII(M3-M5)	91	91	100	96.0	100	161.1	141.8	183.1
Anti-PRN	Czech Republic	HRV	PIII(M3-M5)	182	182	100	98.0	100	112.8	100.5	126.7
		Placebo	PIII(M3-M5)	90	90	100	96.0	100	113.8	97.0	133.5
	France	HRV	PIII(M3-M5)	82	82	100	95.6	100	101.4	85.2	120.8
		Placebo	PIII(M3-M5)	43	43	100	91.8	100	110.7	82.5	148.7
	Germany	HRV	PIII(M3-M5)	155	147	94.8	90.1	97.7	73.6	59.8	90.6
		Placebo	PIII(M3-M5)	84	82	97.6	91.7	99.7	75.6	57.2	100.0
	Spain	HRV	PIII(M3-M5)	188	188	100	98.1	100	105.3	94.3	117.5
		Placebo	PIII(M3-M5)	91	91	100	96.0	100	106.7	89.7	126.9

Infanrix Hexa was administered at: 3, 4, 5 months of age in Czech Republic; 2, 3, 4 months of age in France (Infanrix Polio Hib given at Dose 2) and Germany; 2, 4, 6 months of age in Spain
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3 for Czech Republic, France and Germany; Visit 4 for Spain)

8.2.2.5. Antibody response to HBs

Anti-HBs antibody GMCs and seroprotection rates post Dose 3 of childhood vaccinations are presented in Table 38. Supplement 201 to Supplement 204 present post Dose 3 RCCs for anti-HBs antibody concentrations.

In each country, post Dose 3 anti-HBs antibody GMCs and seroprotection rates were similar in both groups.

Table 38 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 3 of childhood vaccinations - ATP cohort for immunogenicity

				≥ 10 mIU/ml				GMC (mIU/ml)		
						95% CI			95% CI	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Czech Republic	**HRV**	**PIII(M3-M5)**	181	177	97.8	94.4	99.4	408.6	330.2	505.6
	Placebo	**PIII(M3-M5)**	90	88	97.8	92.2	99.7	329.4	248.7	436.4
France	**HRV**	**PII(M3-M4)**	80	77	96.3	89.4	99.2	401.4	281.9	571.7
	Placebo	**PII(M3-M4)**	43	42	97.7	87.7	99.9	481.9	290.9	798.3
Germany	**HRV**	**PIII(M3-M5)**	152	119	78.3	70.9	84.6	143.2	102.1	200.8
	Placebo	**PIII(M3-M5)**	82	65	79.3	68.9	87.4	117.7	76.5	181.0
Spain	**HRV**	**PIII(M3-M5)**	187	184	98.4	95.4	99.7	832.5	676.2	1025.0
	Placebo	**PIII(M3-M5)**	90	85	94.4	87.5	98.2	861.3	589.6	1258.2

Infanrix Hexa was administered at: 3, 4, 5 months of age in Czech Republic; 2, 3, 4 months of age in France (Infanrix Polio Hib given at Dose 2) and Germany; 2, 4, 6 months of age in Spain
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3 for Czech Republic, France and Germany; Visit 4 for Spain)

8.2.2.6. Antibody response to poliovirus types 1, 2 and 3

Anti-poliovirus 1, anti-poliovirus 2 and anti-poliovirus 3 antibody GMTs and seroprotection rates post Dose 3 of childhood vaccinations are presented in Table 39. Supplement 205 to Supplement 216 present post Dose 3 RCC for anti-poliovirus 1, anti-poliovirus 2 and anti-poliovirus 3 antibody titers.

In each country, post Dose 3 anti-poliovirus 1, anti-poliovirus 2 and anti-poliovirus 3 antibody GMTs and seroprotection rates were similar in both groups.

Table 39 Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies post Dose 3 of childhood vaccinations - ATP cohort for immunogenicity

					≥ 8 ED50				GMT		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-poliovirus type 1	Czech Republic	HRV	PIII(M3-M5)	122	122	100	97.0	100	445.5	343.4	578.0
		Placebo	PIII(M3-M5)	65	65	100	94.5	100	370.0	274.2	499.2
	France	HRV	PIII(M3-M5)	44	44	100	92.0	100	89.7	58.9	136.6
		Placebo	PIII(M3-M5)	30	29	96.7	82.8	99.9	142.3	75.5	268.3
	Germany	HRV	PIII(M3-M5)	108	99	91.7	84.8	96.1	119.1	82.0	173.0
		Placebo	PIII(M3-M5)	60	55	91.7	81.6	97.2	85.4	54.7	133.3
	Spain	HRV	PIII(M3-M5)	123	123	100	97.0	100	661.7	533.0	821.5
		Placebo	PIII(M3-M5)	58	58	100	93.8	100	590.9	438.6	796.2
Anti-poliovirus type 2	Czech Republic	HRV	PIII(M3-M5)	124	124	100	97.1	100	376.5	288.7	491.1
		Placebo	PIII(M3-M5)	59	57	96.6	88.3	99.6	269.8	173.1	420.6
	France	HRV	PIII(M3-M5)	44	41	93.2	81.3	98.6	52.5	33.2	82.8
		Placebo	PIII(M3-M5)	29	27	93.1	77.2	99.2	49.8	26.5	93.4
	Germany	HRV	PIII(M3-M5)	110	92	83.6	75.4	90.0	62.0	43.1	89.1
		Placebo	PIII(M3-M5)	62	51	82.3	70.5	90.8	51.7	32.6	82.2
	Spain	HRV	PIII(M3-M5)	118	117	99.2	95.4	100	402.6	310.7	521.8
		Placebo	PIII(M3-M5)	57	57	100	93.7	100	267.1	185.0	385.6
Anti-poliovirus type 3	Czech Republic	HRV	PIII(M3-M5)	114	114	100	96.8	100	1153.0	884.4	1503.1
		Placebo	PIII(M3-M5)	65	65	100	94.5	100	970.6	696.6	1352.5
	France	HRV	PIII(M3-M5)	44	44	100	92.0	100	217.3	128.9	366.1
		Placebo	PIII(M3-M5)	30	30	100	88.4	100	189.8	101.6	354.6
	Germany	HRV	PIII(M3-M5)	109	98	89.9	82.7	94.9	211.5	138.1	323.9
		Placebo	PIII(M3-M5)	59	52	88.1	77.1	95.1	107.2	60.8	189.1
	Spain	HRV	PIII(M3-M5)	120	117	97.5	92.9	99.5	1126.3	854.2	1485.2
		Placebo	PIII(M3-M5)	53	53	100	93.3	100	880.8	596.0	1301.8

Infanrix Hexa was administered at: 3, 4, 5 months of age in Czech Republic; 2, 3, 4 months of age in France (Infanrix Polio Hib given at Dose 2) and Germany; 2, 4, 6 months of age in Spain
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3 for Czech Republic, France and Germany; Visit 4 for Spain)

8.2.2.7. Antibody response to PRP

Anti-PRP antibody GMCs and seroprotection rates post Dose 3 of childhood vaccinations are presented in Table 40. Supplement 217 to Supplement 220 present post Dose 3 RCCs for anti-PRP antibody concentrations.

In each country, the percentages of subjects with anti-PRP concentration ≥ 0.15 µg/ml and ≥ 1.0 µg/ml and GMCs at post Dose 3 of childhood vaccinations were similar in both groups.

Table 40 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 3 of childhood vaccinations - ATP cohort for immunogenicity

				≥ 0.15 µg/ml				≥ 1.0 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Czech Republic	HRV	PIII(M3-M5)	182	179	98.4	95.3	99.7	139	76.4	69.5	82.3	2.862	2.349	3.486
	Placebo	PIII(M3-M5)	90	90	100	96.0	100	65	72.2	61.8	81.1	2.264	1.746	2.937
France	HRV	PIII(M3-M5)	80	76	95.0	87.7	98.6	46	57.5	45.9	68.5	1.388	1.006	1.916
	Placebo	PIII(M3-M5)	43	42	97.7	87.7	99.9	26	60.5	44.4	75.0	1.385	0.955	2.007
Germany	HRV	PIII(M3-M5)	154	133	86.4	79.9	91.4	93	60.4	52.2	68.2	1.344	1.028	1.757
	Placebo	PIII(M3-M5)	83	68	81.9	72.0	89.5	50	60.2	48.9	70.8	1.098	0.751	1.604
Spain	HRV	PIII(M3-M5)	187	182	97.3	93.9	99.1	148	79.1	72.6	84.7	2.796	2.268	3.447
	Placebo	PIII(M3-M5)	91	85	93.4	86.2	97.5	71	78.0	68.1	86.0	2.607	1.873	3.630

Infanrix Hexa was administered at: 3, 4, 5 months of age in Czech Republic; 2, 3, 4 months of age in France (Infanrix Polio Hib given at Dose 2) and Germany; 2, 4, 6 months of age in Spain

N = number of subjects with available results

n/% = number/percentage of subjects with concentration above the cut-off

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PIII(M3-M5) = post Dose 3 of childhood vaccinations (Visit 3 for Czech Republic, France and Germany; Visit 4 for Spain)

8.2.2.8. Evaluation of the differences between groups

Supplement 221 to Supplement 233 present the asymptotic standardized 95% CI on the difference in the post Dose 3 seropositivity/seroprotection rates for antibodies to each antigen in the childhood vaccinations between the groups.

- For Czech Republic, France, Germany and Spain, a statistically significant difference was not detected between the two groups for post Dose 3 seropositivity rate /seroprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, 7 *Streptococcus pneumoniae* serotypes (France and Germany), and SBA-MenC and PSC (Spain) since the two-sided asymptotic standardized 95% CIs for the treatment differences (placebo minus HRV) contain the value zero, except for anti-poliovirus type 2 antibody in Czech Republic (higher response for the HRV vaccine group).

Supplement 234 to Supplement 242 present the 95% CI for the ratios of post Dose 3 GMCs/GMTs for antibodies to each antigen in the childhood vaccinations between the groups.

- For Czech Republic, France, Germany and Spain, a statistically significant difference was not detected between the two groups for post Dose 3 GMCs/GMTs of antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, 7 *Streptococcus pneumoniae* serotypes (France and Germany), and SBA-MenC and PSC (Spain) since the 95% CI for the ratios of GMC/GMT (placebo over HRV) for each antibody contain the value one.

8.2.3. Post-hoc analysis of post Dose 3 immunogenicity of childhood vaccinations in Germany

Post Dose 3 immunogenicity of childhood vaccinations tended to be lower in Germany. Two factors might explain the lower response observed in Germany. Firstly, the interval between the last dose and the blood sample was less than 21 days for 25% of subjects (see Section 8.2.2). The ATP analysis for immunogenicity of co-administered childhood vaccinations) did not exclude any subjects for not respecting the protocol-specified time interval between Dose 3 of childhood vaccinations and the post Dose 3 blood sampling or subjects who had not received 3 doses of the childhood vaccinations because the objective of evaluating immunogenicity of childhood vaccinations was to compare response between HRV vaccine and Placebo groups. The percentage of subjects who received 1, 2 or 3 doses of routine were similar between the two groups (Supplement 33 and Supplement 34). Secondly, investigations into reasons for the lower response in Germany also indicated that the lower response may have been due to center-specific issues at one particular center, Center [redacted] where a total of 60 subjects were enrolled. In view of these findings, post-hoc descriptive analysis was performed to evaluate the post Dose 3 immunogenicity of childhood vaccinations specifically for Center [redacted] and for the German cohort excluding Center [redacted] Only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample were included in these analyses. The results of these analyses are presented in Section 8.2.3.1 and 8.2.3.2 respectively.

Anti-rotavirus IgA response was also evaluated for this center separately and no diminished IgA response was seen for Center [redacted] (these results are available on file at GSK Biologicals, Rixensart).

8.2.3.1. Post Dose 3 immunogenicity of childhood vaccinations for German Center [redacted]

Table 41 to Table 46 present post Dose 3 antibody responses to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP and *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 for subjects from the German Center [redacted] who had received 3 doses of childhood vaccines up to 21 days before the post Dose 3 blood sample.

The immune response to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3 and PRP was much lower in both groups for subjects enrolled at Center [redacted] in Germany.

Table 41 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, and from center [redacted] - ATP cohort for immunogenicity

				≥ 0.1 IU/ml				GMC (IU/ml)		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-diphtheria	**HRV**	**PIII(M3)**	22	18	81.8	59.7	94.8	0.591	0.312	1.120
	Placebo	**PIII(M3)**	9	8	88.9	51.8	99.7	0.407	0.133	1.247
Anti-tetanus	**HRV**	**PIII(M3)**	22	20	90.9	70.8	98.9	0.374	0.213	0.659
	Placebo	**PIII(M3)**	9	9	100	66.4	100	0.385	0.212	0.699

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 42 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, and from center [redacted] - ATP cohort for immunogenicity

				≥ 5 EL.U/ml				GMC (EL.U/ml)		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PT	**HRV**	**PIII(M3)**	21	12	57.1	34.0	78.2	8.5	4.9	14.7
	Placebo	**PIII(M3)**	9	7	77.8	40.0	97.2	10.3	4.8	22.2
Anti-FHA	**HRV**	**PIII(M3)**	22	20	90.9	70.8	98.9	28.0	13.5	58.3
	Placebo	**PIII(M3)**	9	7	77.8	40.0	97.2	18.2	5.5	60.4
Anti-PRN	**HRV**	**PIII(M3)**	22	17	77.3	54.6	92.2	17.4	9.0	33.6
	Placebo	**PIII(M3)**	9	8	88.9	51.8	99.7	22.5	7.8	65.1

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 43 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, and from center [redacted] - ATP cohort for immunogenicity

				≥ 10 mIU/ml				GMC (mIU/ml)		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-HBs	**HRV**	**PIII(M3)**	22	8	36.4	17.2	59.3	15.7	7.1	35.0
	Placebo	**PIII(M3)**	9	2	22.2	2.8	60.0	10.1	3.5	29.6

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 44 Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, and from center [redacted] - ATP cohort for immunogenicity

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-poliovirus type 1	**HRV**	**PIII(M3)**	21	15	71.4	47.8	88.7	24.9	10.4	59.7
	Placebo	**PIII(M3)**	8	7	87.5	47.3	99.7	30.7	9.7	97.5
Anti-poliovirus type 2	**HRV**	**PIII(M3)**	19	11	57.9	33.5	79.7	13.5	5.9	30.8
	Placebo	**PIII(M3)**	9	6	66.7	29.9	92.5	14.3	6.1	33.3
Anti-poliovirus type 3	**HRV**	**PIII(M3)**	18	12	66.7	41.0	86.7	23.9	8.7	65.7
	Placebo	**PIII(M3)**	9	7	77.8	40.0	97.2	21.0	6.3	69.4

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with titre above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 45 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, and from center [redacted] - ATP cohort for immunogenicity

				≥ 0.15 µg/ml				≥ 1 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PRP	**HRV**	**PIII(M3)**	22	13	59.1	36.4	79.3	5	22.7	7.8	45.4	0.356	0.164	0.774
	Placebo	**PIII(M3)**	9	3	33.3	7.5	70.1	2	22.2	2.8	60.0	0.207	0.059	0.723

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 46 Seropositivity rates and GMCs for antibodies to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, and from center [redacted] - ATP cohort for immunogenicity

				≥ 0.05 µg/ml				≥ 0.2 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Pneumonia serotype 4	HRV	PIII(M3)	22	22	100	84.6	100	22	100	84.6	100	3.58	2.74	4.68
	Placebo	PIII(M3)	9	9	100	66.4	100	9	100	66.4	100	4.22	2.27	7.85
Pneumonia serotype 6B	HRV	PIII(M3)	22	18	81.8	59.7	94.8	12	54.5	32.2	75.6	0.24	0.12	0.48
	Placebo	PIII(M3)	9	3	33.3	7.5	70.1	3	33.3	7.5	70.1	0.08	0.02	0.28
Pneumonia serotype 9V	HRV	PIII(M3)	22	22	100	84.6	100	22	100	84.6	100	2.76	1.76	4.34
	Placebo	PIII(M3)	9	9	100	66.4	100	9	100	66.4	100	2.94	1.54	5.63
Pneumonia serotype 14	HRV	PIII(M3)	22	22	100	84.6	100	22	100	84.6	100	4.24	3.00	5.99
	Placebo	PIII(M3)	9	9	100	66.4	100	9	100	66.4	100	2.67	0.95	7.54
Pneumonia serotype 18C	HRV	PIII(M3)	22	22	100	84.6	100	21	95.5	77.2	99.9	2.11	1.28	3.49
	Placebo	PIII(M3)	9	9	100	66.4	100	9	100	66.4	100	2.40	1.11	5.22
Pneumonia serotype 19F	HRV	PIII(M3)	22	22	100	84.6	100	22	100	84.6	100	3.60	2.06	6.28
	Placebo	PIII(M3)	9	9	100	66.4	100	9	100	66.4	100	3.89	1.63	9.32
Pneumonia serotype 23F	HRV	PIII(M3)	22	16	72.7	49.8	89.3	16	72.7	49.8	89.3	0.47	0.19	1.15
	Placebo	PIII(M3)	9	6	66.7	29.9	92.5	3	33.3	7.5	70.1	0.18	0.02	1.30

Prevenar was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

8.2.3.2. Post Dose 3 immunogenicity of childhood vaccinations for Germany excluding Center [redacted]

Table 53 to Table 57 present post Dose 3 antibody responses to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP and *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 for subjects in Germany who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from Center [redacted]

Post Dose 3 immunogenicity of childhood in Germany was much improved when Center [redacted] was excluded from analysis.

When Center [redacted] was excluded from analysis for Germany, 100% of subjects in the HRV vaccine group had seroprotective levels of anti-diphtheria, anti-tetanus and anti-poliovirus types 1, 2 and 3 antibodies. All subjects had anti-PT, anti-FHA and anti-PRN antibody concentration ≥ 5 EL.U/ml. Seroprotective levels of anti-HBs antibodies were observed in 94.5% of subjects in the HRV vaccine group and 100% in the Placebo groups. Seroprotection rate for anti-PRP antibodies was similarly high in both groups. The majority of subjects had antibody concentration of ≥ 0.05 µg/ml for antibodies against each of the seven pneumococcal serotypes.

Seroprotection/seropositivity rates and GMCs/GMTs for antibodies to all co-administered antigens are similar between the two groups and these results are consistent with other countries.

Table 47 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from center [redacted] - ATP cohort for immunogenicity

				≥ 0.1 IU/ml				GMC (IU/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	HRV	PIII(M3)	94	94	100	96.2	100	1.981	1.638	2.397
	Placebo	PIII(M3)	52	52	100	93.2	100	1.890	1.463	2.442
Anti-tetanus	HRV	PIII(M3)	94	94	100	96.2	100	1.713	1.467	2.000
	Placebo	PIII(M3)	52	52	100	93.2	100	1.633	1.322	2.016

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 48 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from center [redacted] - ATP cohort for immunogenicity

				≥ 5 EL.U/ml				GMC (EL.U/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	HRV	PIII(M3)	94	94	100	96.2	100	46.3	41.4	51.8
	Placebo	PIII(M3)	52	52	100	93.2	100	42.2	36.3	49.0
Anti-FHA	HRV	PIII(M3)	94	94	100	96.2	100	203.2	180.4	228.9
	Placebo	PIII(M3)	52	52	100	93.2	100	181.0	153.9	212.8
Anti-PRN	HRV	PIII(M3)	94	94	100	96.2	100	119.9	100.6	142.9
	Placebo	PIII(M3)	52	52	100	93.2	100	117.0	89.4	153.3

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 49 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from center [redacted] - ATP cohort for immunogenicity

				≥ 10 mIU/ml				GMC (mIU/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-HBs	HRV	PIII(M3)	91	86	94.5	87.6	98.2	298.8	218.1	409.6
	Placebo	PIII(M3)	52	52	100	93.2	100	318.9	235.3	432.1

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 50 Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from center [redacted] - ATP cohort for immunogenicity

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-poliovirus type 1	HRV	PIII(M3)	59	59	100	93.9	100	379.8	276.7	521.3
	Placebo	PIII(M3)	37	37	100	90.5	100	176.0	110.8	279.5
Anti-poliovirus type 2	HRV	PIII(M3)	64	64	100	94.4	100	153.1	107.8	217.5
	Placebo	PIII(M3)	37	36	97.3	85.8	99.9	119.7	70.8	202.6
Anti-poliovirus type 3	HRV	PIII(M3)	65	65	100	94.5	100	727.8	510.0	1038.7
	Placebo	PIII(M3)	35	35	100	90.0	100	372.8	223.8	621.2

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with titer above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 51 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from center [redacted] - ATP cohort for immunogenicity

				≥ 0.15 µg/ml				≥ 1 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Anti-PRP	HRV	PIII(M3)	93	92	98.9	94.2	100	71	76.3	66.4	84.5	2.431	1.868	3.164
	Placebo	PIII(M3)	52	48	92.3	81.5	97.9	38	73.1	59.0	84.4	1.746	1.166	2.615

Infanrix Hexa was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

Table 52 Seropositivity rates and GMCs for antibodies to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 of childhood vaccinations – Germany, only subjects who received 3 doses of childhood vaccinations up to 21 days before the blood sample, excluding those from center [redacted] - ATP cohort for immunogenicity

				≥ 0.05 µg/ml				≥ 0.2 µg /ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Pneumonia serotype 4	**HRV**	**PIII(M3)**	94	94	100	96.2	100	94	100	96.2	100	2.98	2.54	3.50
	Placebo	**PIII(M3)**	52	52	100	93.2	100	52	100	93.2	100	2.68	2.13	3.39
Pneumonia serotype 6B	**HRV**	**PIII(M3)**	94	90	95.7	89.5	98.8	78	83.0	73.8	89.9	0.83	0.61	1.13
	Placebo	**PIII(M3)**	52	52	100	93.2	100	40	76.9	63.2	87.5	0.76	0.50	1.13
Pneumonia serotype 9V	**HRV**	**PIII(M3)**	94	94	100	96.2	100	94	100	96.2	100	3.08	2.65	3.58
	Placebo	**PIII(M3)**	52	52	100	93.2	100	52	100	93.2	100	2.23	1.75	2.84
Pneumonia serotype 14	**HRV**	**PIII(M3)**	94	94	100	96.2	100	93	98.9	94.2	100	4.87	4.01	5.92
	Placebo	**PIII(M3)**	52	52	100	93.2	100	51	98.1	89.7	100	4.11	2.83	5.96
Pneumonia serotype 18C	**HRV**	**PIII(M3)**	94	94	100	96.2	100	94	100	96.2	100	4.29	3.54	5.20
	Placebo	**PIII(M3)**	52	52	100	93.2	100	50	96.2	86.8	99.5	3.44	2.50	4.73
Pneumonia serotype 19F	**HRV**	**PIII(M3)**	94	94	100	96.2	100	94	100	96.2	100	3.69	3.08	4.42
	Placebo	**PIII(M3)**	52	52	100	93.2	100	52	100	93.2	100	3.09	2.54	3.75
Pneumonia serotype 23F	**HRV**	**PIII(M3)**	94	94	100	96.2	100	91	96.8	91.0	99.3	2.18	1.72	2.76
	Placebo	**PIII(M3)**	52	52	100	93.2	100	49	94.2	84.1	98.8	1.82	1.29	2.56

Prevenar was administered 2, 3, 4 months of age in Germany
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3) = post Dose 3 of childhood vaccinations (Visit 3)

8.2.4. Post Dose 2 immunogenicity of childhood vaccinations in Finland, Italy and Spain

In Finland, Italy and Spain, the immunogenicity of the co-administered childhood vaccinations was also assessed after the first 2 doses of the childhood vaccinations which is an intermediate timepoint after an incomplete vaccination course of childhood vaccinations.

Post Dose 2 immunogenicity results for childhood vaccinations are presented in Supplement 243 to Supplement 281. Post Dose 2 seroprotection/seropositivity rates and GMCs/GMTs for antibodies to each antigen were similar between the two groups in each country.

Supplement 282 to Supplement 300 present evaluation of differences between groups for post Dose 2 response to each antigen in the childhood vaccinations.

- For Finland, Italy and Spain, a statistically significant difference was not detected between the two groups for post Dose 2 seropositivity rate /seroprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, and SBA-MenC and PSC (Spain) since the two-sided asymptotic standardized 95% CIs for the treatment differences (placebo minus HRV) contain the value zero, except for anti-PRP antibody in Finland (higher response for the HRV vaccine group).
- For Finland, Italy and Spain, a statistically significant difference was not detected between the two groups for post Dose 2 GMC/GMT for antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP, and SBA-MenC and PSC (Spain) since the 95% CI for the ratios of GMC/GMT (placebo over HRV) for each antibody contain the value one, except for anti-poliovirus type 3 antibody in Finland and in Spain (higher response for the HRV vaccine group).

8.3. Total vaccinated cohort for the immunogenicity and reactogenicity subset

Supplement 301 to Supplement 319 present immunogenicity results for the total vaccinated cohort for the immunogenicity and reactogenicity subset.

The immunogenicity results of the total vaccinated cohort analysis were consistent with those obtained for the ATP analysis.

8.3.1. Post Dose 3 immunogenicity of childhood vaccinations in Finland (interim analysis on the total vaccinated cohort of the immunogenicity and reactogenicity subset in Finland)

The two first doses of Infanrix Hexa were co-administered with each HRV vaccine or placebo dose in Finland. Subjects were to receive the 3rd dose of childhood vaccination series as per the recommended national schedule (without HRV).

Table 53 to Table 57 present the antibody responses to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP post Dose 3 of childhood vaccinations in Finland.

A high level of seroprotection rate for anti-diphtheria, anti-tetanus, anti-HBs, anti-poliovirus 1, anti-poliovirus 2 and anti-poliovirus 3 antibodies was observed in both groups at post Dose 3 of childhood vaccinations in Finland. All subjects had anti-PT, anti-FHA and anti-PRN antibody concentration ≥ 5 EL.U/ml. All subjects had anti-PRP antibody concentration ≥ 0.15 µg/ml. 97.1% of subjects in the HRV vaccine group and 99.1% of subjects in the Placebo group had anti-PRP antibody concentration ≥ 1.0 µg/ml. Seroprotection/seropositivity rates and GMCs/GMTs for antibodies to each antigen were similar between the two groups.

Table 53 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccinations in Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

			≥ 0.1 IU/ml					GMC (IU/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	HRV	PIII(M10)	175	174	99.4	96.9	100	2.810	2.439	3.239
	Placebo	PIII(M10)	107	107	100	96.6	100	2.548	2.189	2.967
Anti-tetanus	HRV	PIII(M10)	175	175	100	97.9	100	5.601	5.087	6.167
	Placebo	PIII(M10)	107	107	100	96.6	100	5.017	4.430	5.682

Infanrix Hexa was administered at: 3, 5, 11-12 months of age in Finland
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M10) = post Dose 3 of childhood vaccinations (Visit 6)

Table 54 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 3 of childhood vaccinations in Finland – Total vaccinated cohort for the reactogenicity and immunogenicity subset

			≥ 5 EL.U/ml					GMC (EL.U/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	HRV	PIII(M10)	175	175	100	97.9	100	94.5	87.2	102.4
	Placebo	PIII(M10)	107	107	100	96.6	100	81.5	72.6	91.4
Anti-FHA	HRV	PIII(M10)	175	175	100	97.9	100	549.4	503.5	599.5
	Placebo	PIII(M10)	107	107	100	96.6	100	476.2	424.4	534.4
Anti-PRN	HRV	PIII(M10)	175	175	100	97.9	100	309.8	277.8	345.3
	Placebo	PIII(M10)	107	107	100	96.6	100	307.7	267.8	353.5

Infanrix Hexa was administered at: 3, 5, 11-12 months of age in Finland
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M10) = post Dose 3 of childhood vaccinations (Visit 6)

Table 55 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 3 of childhood vaccinations in Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

		≥ 10 mIU/ml					GMC (mIU/ml)		
					95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HRV	**PIII(M10)**	174	174	100	97.9	100	6637.9	5580.8	7895.2
Placebo	**PIII(M10)**	107	107	100	96.6	100	5622.9	4355.5	7259.1

Infanrix Hexa was administered at: 3, 5, 11-12 months of age in Finland
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M10) = post Dose 3 of childhood vaccinations (Visit 6)

Table 56 Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies post Dose 3 of childhood vaccinations in Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

			≥ 8 ED50					GMT		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-poliovirus type 1	**HRV**	**PIII(M10)**	146	146	100	97.5	100	1102.2	899.0	1351.4
	Placebo	**PIII(M10)**	99	99	100	96.3	100	899.8	699.1	1158.0
Anti-poliovirus type 2	**HRV**	**PIII(M10)**	142	142	100	97.4	100	585.8	445.5	770.4
	Placebo	**PIII(M10)**	93	93	100	96.1	100	322.8	226.3	460.6
Anti-poliovirus type 3	**HRV**	**PIII(M10)**	138	138	100	97.4	100	1430.0	1104.1	1852.0
	Placebo	**PIII(M10)**	86	85	98.8	93.7	100	1066.1	751.3	1513.0

Infanrix Hexa was administered at: 3, 5, 11-12 months of age in Finland
N = number of subjects with available results
n/% = number/percentage of subjects with titre above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M10) = post Dose 3 of childhood vaccinations (Visit 6)

Table 57 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 3 of childhood vaccinations in Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

		≥ 0.15 µg/ml					≥ 1 µg/ml				GMC (µg/ml)		
					95% CI				95% CI			95% CI	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HRV	**PIII(M10)**	174	174	100	97.9	100	169	97.1	93.4	99.1	16.838	14.145	20.043
Placebo	**PIII(M10)**	107	107	100	96.6	100	106	99.1	94.9	100	11.951	9.622	14.843

Infanrix Hexa was administered at: 3, 5, 11-12 months of age in Finland
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M10) = post Dose 3 of childhood vaccinations (Visit 6)

8.3.2. Post Dose 3 immunogenicity of childhood vaccinations in Italy (interim analysis on the total vaccinated cohort of the immunogenicity and reactogenicity subset in Italy)

The two first doses of Infanrix Hexa were co-administered with each HRV vaccine or placebo dose in Italy. Subjects were to receive the 3rd dose of childhood vaccination series as per the recommended national schedule (without HRV).

Table 58 to Table 62 present the antibody responses to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP post Dose 3 of childhood vaccinations in Italy.

In the small immunogenicity subset from Italy, all subjects in each group had seroprotective levels of anti-diphtheria, anti-tetanus, anti-HBs (except one subject in the placebo group who did not have seroprotective levels), anti-poliovirus 1, anti-poliovirus 2, anti-poliovirus 3 and anti-PRP antibodies, and were seropositive for anti-PT, anti-FHA and anti-PRN antibodies at post Dose 3 of childhood vaccinations in Italy.

Table 58 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccinations in Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.1 IU/ml				GMC (IU/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	HRV	PIII(M9)	14	14	100	76.8	100	6.492	4.353	9.682
	Placebo	PIII(M9)	10	10	100	69.2	100	7.360	4.795	11.297
Anti-tetanus	HRV	PIII(M9)	14	14	100	76.8	100	6.390	4.219	9.676
	Placebo	PIII(M9)	10	10	100	69.2	100	6.298	3.573	11.101

Infanrix Hexa was administered at: 3, 5, 11 months of age in Italy
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M9) = post Dose 3 of routine childhood vaccinations (Visit 6)

Table 59 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 3 of childhood vaccinations in Italy – Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 5 EL.U/ml				GMC (EL.U/ml)		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	HRV	PIII(M9)	14	14	100	76.8	100	74.0	44.8	122.3
	Placebo	PIII(M9)	10	10	100	69.2	100	78.8	64.0	97.0
Anti-FHA	HRV	PIII(M9)	14	14	100	76.8	100	500.8	339.8	738.3
	Placebo	PIII(M9)	10	10	100	69.2	100	495.8	364.5	674.2
Anti-PRN	HRV	PIII(M9)	14	14	100	76.8	100	310.7	201.2	479.7
	Placebo	PIII(M9)	10	10	100	69.2	100	327.0	225.0	475.2

Infanrix Hexa was administered at: 3, 5, 11 months of age in Italy
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M9) = post Dose 3 of routine childhood vaccinations (Visit 6)

Table 60 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 3 of childhood vaccinations in Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

			≥ 10 mIU/ml				GMC (mIU/ml)		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV	PIII(M9)	14	14	100	76.8	100	3977.0	1937.0	8165.5
Placebo	PIII(M9)	9	8	88.9	51.8	99.7	2398.7	362.2	15886.5

Infanrix Hexa was administered at: 3, 5, 11 months of age in Italy
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M9) = post Dose 3 of routine childhood vaccinations (Visit 6)

Table 61 Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies post Dose 3 of childhood vaccinations in Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-poliovirus type 1	HRV	PIII(M9)	5	5	100	47.8	100	3326.9	928.1	11925.2
	Placebo	PIII(M9)	4	4	100	39.8	100	3158.4	929.8	10728.8
Anti-poliovirus type 2	HRV	PIII(M9)	6	6	100	54.1	100	4597.6	1748.4	12090.1
	Placebo	PIII(M9)	4	4	100	39.8	100	4466.8	1741.6	11456.0
Anti-poliovirus type 3	HRV	PIII(M9)	6	6	100	54.1	100	4095.9	1296.6	12938.1
	Placebo	PIII(M9)	4	4	100	39.8	100	2655.9	197.0	35804.4

Infanrix Hexa was administered at: 3, 5, 11 months of age in Italy
N = number of subjects with available results
n/% = number/percentage of subjects with titre above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M9) = post Dose 3 of routine childhood vaccinations (Visit 6)

Table 62 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 3 of childhood vaccinations in Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

			≥ 0.15 µg/ml				≥ 1 µg/ml				GMC (µg/ml)		
					95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HRV	PIII(M9)	14	14	100	76.8	100	14	100	76.8	100	13.343	7.259	24.524
Placebo	PIII(M9)	10	10	100	69.2	100	10	100	69.2	100	15.097	5.404	42.174

Infanrix Hexa was administered at: 3, 5, 11 months of age in Italy
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M9) = post Dose 3 of routine childhood vaccinations (Visit 6)

8.4. Immunogenicity conclusions

- GSK Biologicals' HRV vaccine was immunogenic as shown by the anti-rotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%) observed in the HRV vaccine group at one to two months after Dose 2.

- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of any antigens contained in each of the co-administered childhood vaccinations (Infanrix Hexa, Infanrix Polio Hib, Prevenar or Meningitec).

9. SAFETY RESULTS

9.1. Data sets analyzed

The analysis of safety (unsolicited AEs and SAEs) was performed on the total vaccinated cohort. The analysis of reactogenicity was performed on the total vaccinated cohort for the immunogenicity and reactogenicity subset. See Section 5.9.4 for the definition of the cohorts identified for analyses and Section 6.2.3.1 for eligibility for analyses.

The analyses of reactogenicity and safety planned numerous group comparisons through P-value computation. The P-values were used as an aid to highlight potential imbalances worth further attention (significance level of alpha = 0.05) and care was to be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment, and the rate of false signals could be considerably large due to the number of comparisons. When a potential imbalance between groups was noted, individual AE cases were reviewed by a sponsor physician and conclusions were based on clinical judgement.

9.2. Total vaccinated cohort analysis

Table 63 presents the number and percentage of subjects who received HRV vaccine or placebo doses.

Table 63 Number and percentage of subjects who received HRV vaccine/placebo dose(s) – Pooled countries – Total vaccinated cohort

	HRV N = 2646		Placebo N = 1348		Total N = 3994	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	25	0.9	10	0.7	35	0.9
2	2621	99.1	1338	99.3	3959	99.1
At least one	2646	100	1348	100	3994	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV vaccine/placebo

The number and percentage of subjects who received HRV vaccine or placebo doses per country are presented in Supplement 320 to Supplement 325.

Majority (at least 98.5%) of subjects received childhood vaccinations with each dose of HRV vaccine or placebo (see Section 6.4).

9.3. Total vaccinated cohort for the immunogenicity and reactogenicity subset

Reactogenicity was evaluated in the immunogenicity and reactogenicity subset which included 1404 subjects (subset of 300 subjects from Finland and all enrolled subjects from the other countries).

The number of doses given and the number of completed symptom sheets (see definition in glossary of terms) for the total vaccinated cohort for the immunogenicity and reactogenicity subset (pooled countries) are detailed in Supplement 326. The same information for each country is provided in Supplement 327 to Supplement 332.

Symptom sheets were completed for the majority of doses in each group (99.4% in the HRV vaccine group and 99.7% in the Placebo group), indicating high compliance for reactogenicity reporting.

9.3.1. Overall incidence of adverse events

Table 64 presents the percentage of doses and of subjects with any symptom (solicited or unsolicited) reported from Day 0 to Day 7 after any HRV vaccine/placebo doses.

Supplement 333 presents the percentage of doses and of subjects with grade "3" symptoms (solicited or unsolicited) reported from Day 0 to Day 7 after any HRV vaccine/placebo doses and Supplement 334 presents the percentage of doses and of subjects with symptoms (solicited or unsolicited) assessed as related to vaccination reported from Day 0 to Day 7 after any HRV vaccine/placebo doses.

From Day 0 to Day 7 after any HRV vaccine/placebo doses, the percentage of subjects with symptoms (solicited and unsolicited) were similar between the two groups. 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.

Table 64 Percentage of doses and of subjects with symptoms (solicited or unsolicited) reported from Day 0 to Day 7 after any HRV vaccine/placebo doses – Pooled countries – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV	914	620	67.8	64.7	70.9
	Placebo	490	330	67.3	63.0	71.5
Dose 2	HRV	905	589	65.1	61.9	68.2
	Placebo	486	327	67.3	62.9	71.4
Overall/dose	HRV	1819	1209	66.5	64.2	68.6
	Placebo	976	657	67.3	64.3	70.3
Overall/subject	HRV	914	736	80.5	77.8	83.0
	Placebo	490	410	83.7	80.1	86.8

For each dose: N = number of subjects having received the considered dose of HRV vaccine/placebo
n/% = number/percentage of subjects with at least one symptom for the considered dose, reported during the specified period
For overall/dose: N = total number of HRV vaccine/placebo doses administered
n/% = number/percentage of doses followed by at least one symptom, during the specified period
For overall/subject: N= number of subjects having received at least one dose of HRV vaccine/placebo
n%= number/percentage of subjects with at least one symptom, reported during the specified period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

9.3.2. Solicited general adverse events

Table 65 presents the percentage of subjects with each solicited general symptom including those graded 3 in intensity and those assessed as causally related to vaccination, reported from Day 0 to Day 7 after each HRV vaccine/placebo dose.

Supplement 335 presents the percentage of doses and of subjects with each solicited general symptoms including those graded 3 in intensity and those assessed as causally related to vaccination, reported from Day 0 to Day 7 after any HRV vaccine/placebo dose.

Supplement 336 to Supplement 341 present prevalence of diarrhea, vomiting and fever by day after each dose during the solicited follow-up period.

- Irritability was the most frequently reported solicited general solicited symptom in both groups after each dose.
- The incidence of grade 3 solicited symptoms was similarly low in both groups.
- The incidence of solicited symptoms did not increase with subsequent doses of HRV vaccine or placebo.
- No peak was observed for the incidence of diarrhea or vomiting after each dose of the HRV vaccine or placebo (see Supplement 336 and Supplement 337 for prevalence of diarrhea, and Supplement 338 and Supplement 339 for prevalence of vomiting).

- A higher incidence of fever was observed on Day 0 and Day 1 after each dose in both groups (see Supplement 340 and Supplement 341). Since incidences are similar between the HRV vaccine and Placebo group, co-administered childhood vaccinations could have contributed to post-vaccination fever. The majority of fever reports were rated as grade 1 or 2; grade 3 fever was reported by only two subjects in the HRV vaccine group and 4 subjects in the Placebo group after Dose 2.

Table 65 Percentage of subjects with each solicited general symptoms, including those graded 3 in intensity and those assessed as causally related to vaccination, reported from Day 0 to Day 7 after each HRV vaccine/placebo dose - Pooled countries – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	914	221	24.2	21.4	27.1	490	117	23.9	20.2	27.9
	Grade 3	914	7	0.8	0.3	1.6	490	2	0.4	0.0	1.5
	Related	914	58	6.3	4.9	8.1	490	29	5.9	4.0	8.4
Diarrhea	Total	914	24	2.6	1.7	3.9	490	11	2.2	1.1	4.0
	Grade 3	914	3	0.3	0.1	1.0	490	4	0.8	0.2	2.1
	Related	914	18	2.0	1.2	3.1	490	7	1.4	0.6	2.9
Fever	Total	914	166	18.2	15.7	20.8	490	91	18.6	15.2	22.3
	Grade 3	914	0	0.0	0.0	0.4	490	0	0.0	0.0	0.8
	Related	914	133	14.6	12.3	17.0	490	67	13.7	10.8	17.0
Irritability/Fussiness	Total	914	460	50.3	47.0	53.6	490	250	51.0	46.5	55.5
	Grade 3	914	23	2.5	1.6	3.8	490	19	3.9	2.4	6.0
	Related	914	299	32.7	29.7	35.9	490	171	34.9	30.7	39.3
Loss of appetite	Total	914	210	23.0	20.3	25.8	490	100	20.4	16.9	24.3
	Grade 3	914	4	0.4	0.1	1.1	490	1	0.2	0.0	1.1
	Related	914	126	13.8	11.6	16.2	490	71	14.5	11.5	17.9
Vomiting	Total	914	101	11.1	9.1	13.3	490	52	10.6	8.0	13.7
	Grade 3	914	10	1.1	0.5	2.0	490	6	1.2	0.5	2.6
	Related	914	44	4.8	3.5	6.4	490	24	4.9	3.2	7.2
Dose 2											
Cough/Runny nose	Total	905	234	25.9	23.0	28.8	486	149	30.7	26.6	35.0
	Grade 3	905	10	1.1	0.5	2.0	486	1	0.2	0.0	1.1
	Related	905	53	5.9	4.4	7.6	486	34	7.0	4.9	9.6
Diarrhea	Total	905	15	1.7	0.9	2.7	486	9	1.9	0.9	3.5
	Grade 3	905	6	0.7	0.2	1.4	486	6	1.2	0.5	2.7
	Related	905	6	0.7	0.2	1.4	486	8	1.6	0.7	3.2
Fever	Total	905	244	27.0	24.1	30.0	486	142	29.2	25.2	33.5
	Grade 3	905	2	0.2	0.0	0.8	486	4	0.8	0.2	2.1
	Related	905	164	18.1	15.7	20.8	486	95	19.5	16.1	23.4
Irritability/Fussiness	Total	905	390	43.1	39.8	46.4	486	215	44.2	39.8	48.8
	Grade 3	905	21	2.3	1.4	3.5	486	7	1.4	0.6	2.9
	Related	905	238	26.3	23.5	29.3	486	123	25.3	21.5	29.4
Loss of appetite	Total	905	195	21.5	18.9	24.4	486	102	21.0	17.5	24.9
	Grade 3	905	6	0.7	0.2	1.4	486	1	0.2	0.0	1.1
	Related	905	118	13.0	10.9	15.4	486	57	11.7	9.0	14.9
Vomiting	Total	905	53	5.9	4.4	7.6	486	46	9.5	7.0	12.4
	Grade 3	905	9	1.0	0.5	1.9	486	7	1.4	0.6	2.9
	Related	905	18	2.0	1.2	3.1	486	23	4.7	3.0	7.0

N = number of subjects having received the considered dose of HRV vaccine/placebo
n/% = number/percentage of subjects with the specified symptom reported for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 66 presents the statistical comparisons between the HRV vaccine group and the Placebo group for the percentage of subjects with each solicited symptom reported from Day 0 to Day 7 after any HRV vaccine/placebo doses.

Statistically significant differences were not detected between groups for the exploratory comparison between the HRV vaccine and Placebo groups for the percentage of subjects with each specified solicited symptom (any, grade 3 and related) reported from Day 0 to Day 7 after any HRV vaccine/placebo doses (P-value > 0.05 for each comparison).

Table 66 Statistical comparisons between groups for the percentage of subjects with each solicited symptom reported from Day 0 to Day 7 after any HRV vaccine/placebo doses - Pooled countries - Total vaccinated cohort for immunogenicity and reactogenicity subset

		HRV			Placebo			
Symptoms	**Type**	**N**	**n**	**%**	**N**	**n**	**%**	**P-value**
Overall/subject								
Cough/Runny nose	Total	914	366	40.0	490	205	41.8	0.531
	Grade 3	914	16	1.8	490	3	0.6	0.092
	Related	914	99	10.8	490	52	10.6	0.928
Diarrhea	Total	914	38	4.2	490	20	4.1	1.000
	Grade 3	914	9	1.0	490	10	2.0	0.143
	Related	914	24	2.6	490	15	3.1	0.614
Fever	Total	914	310	33.9	490	192	39.2	0.054
	Grade 3	914	2	0.2	490	4	0.8	0.192
	Related	914	234	25.6	490	137	28.0	0.342
Irritability/Fussiness	Total	914	567	62.0	490	308	62.9	0.773
	Grade 3	914	40	4.4	490	25	5.1	0.594
	Related	914	395	43.2	490	218	44.5	0.652
Loss of appetite	Total	914	310	33.9	490	161	32.9	0.722
	Grade 3	914	9	1.0	490	2	0.4	0.347
	Related	914	202	22.1	490	107	21.8	0.946
Vomiting	Total	914	131	14.3	490	80	16.3	0.347
	Grade 3	914	18	2.0	490	12	2.4	0.565
	Related	914	56	6.1	490	40	8.2	0.151

N = number of subjects having received at least one dose of HRV vaccine/placebo
n/% = number/percentage of subjects with the specified symptom reported after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
P-value = result of the comparison between groups of the percentages of subjects with the specified solicited symptom reported after any HRV vaccine/placebo doses, by a two-sided Fisher's exact test (P-values less than 0.05 have been used as an aid to highlight potential imbalances worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 342 to Supplement 353 presents reactogenicity data for each country. The results of per country analysis are consistent with the overall reactogenicity results.

9.4. Unsolicited adverse events

Supplement 354 to Supplement 357 present the percentage of subjects and of doses with unsolicited AEs classified by MedDRA SOC and PT from Day 0 to Day 30 after any

HRV vaccine/placebo doses. Supplement 358 to Supplement 361 present the percentage of subjects and of doses with grade 3 unsolicited AEs classified by MedDRA SOC and PT from Day 0 to Day 30 after any HRV vaccine/placebo doses. Supplement 362 to Supplement 365 present the percentage of subjects and of doses with unsolicited AEs assessed as related to vaccination classified by MedDRA SOC and PT from Day 0 to Day 30 after any HRV vaccine/placebo doses.

From Day 0 to Day 30 after any HRV vaccine/placebo doses,

- Unsolicited AEs were reported by 63.7% (95% CI: 61.9%; 65.6%) subjects in the HRV vaccine group and 61.4% (95% CI: 58.8%; 64.0%) subjects in the Placebo group (P-value = 0.156).
- Grade 3 unsolicited AEs were reported by 8.8% (95% CI: 7.8%; 10.0%) subjects in the HRV vaccine group and 8.8% (95% CI: 7.3%; 10.4%) subjects in the Placebo group (P-value = 0.956).
- Unsolicited AEs assessed as related to vaccination were reported by 29.2% (95% CI: 27.4%; 30.9%) subjects in the HRV vaccine group and 27.7% (95% CI: 25.3%; 30.1%) subjects in the Placebo group (P-value = 0.320).

Table 67 presents the percentage of subjects with unsolicited AEs from Day 0 to Day 30 after any HRV vaccine/placebo doses according to MedDRA PTs for which a potential imbalance was noted between the groups (based on a predefined exploratory P-value < 0.05 significance level); The MedDRA SOC linked to these selected PTs are also included in Table 67.

Putative statistically significant findings (P-value < 0.05) should be interpreted cautiously since the observed imbalances are likely to occur by chance alone due to the number of comparisons performed without multiplicity adjustment.

When unsolicited AEs from Day 0 to Day 30 after any HRV vaccine/placebo doses were classified according to the MedDRA SOCs/PTs, potential imbalance between the HRV vaccine group and the Placebo group was seen for the following AEs:

- Potential imbalance in favour of the HRV vaccine was noted for diarrhea, stridor, grade 3 bronchiolitis, grade 3 otitis externa and grade 3 rhinorrhoea. All cases recovered/resolved completely except one case of grade 3 bronchiolitis which recovered/resolved with sequelae.
- Potential imbalance in favour of the Placebo was noted for flatulence, irritability and irritability assessed as related to vaccination. All cases recovered completely.

Individual cases under MedDRA PTs for which a potential imbalance was detected were reviewed by sponsor physicians. Clinical review of individual cases by the sponsor physician gave no evidence of clinically relevant findings indicating that the potential imbalance was possibly a chance finding. It should be noted that the observed potential imbalance between treatment groups based on the specific MedDRA PTs were not observed for the associated primary SOC.

Table 67 Percentage of subjects with unsolicited AEs classified by selected MedDRA SOC and PT from Day 0 to Day 30 after any HRV vaccine/placebo doses - Pooled countries - Total vaccinated cohort

MedDRA PT	HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
			95% CI				95% CI			95% CI*		
	n	%	LL	UL	n	%	LL	UL	%	LL	UL	
Unsolicited AEs												
At least one symptom	1686	63.7	61.9	65.6	828	61.4	58.8	64.0	2.29	-0.87	5.49	0.156
SOC: Gastrointestinal disorders (10017947)	379	14.3	13.0	15.7	171	12.7	11.0	14.6	1.64	-0.64	3.82	0.155
PT: Diarrhea (10012735)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
PT: Flatulence (10016766)	100	3.8	3.1	4.6	33	2.4	1.7	3.4	1.33	0.17	2.40	0.027
SOC: General disorders and administration site conditions (10018065)	1009	38.1	36.3	40.0	477	35.4	32.8	38.0	2.75	-0.43	5.88	0.089
PT: Irritability (10022998)	555	21.0	19.4	22.6	229	17.0	15.0	19.1	3.99	1.41	6.48	0.003
SOC: Respiratory, thoracic and mediastinal disorders (10038738)	199	7.5	6.5	8.6	105	7.8	6.4	9.4	-0.27	-2.08	1.43	0.762
PT: Stridor (10042241)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
Grade 3 unsolicited AEs												
At least one symptom	233	8.8	7.8	10.0	118	8.8	7.3	10.4	0.05	-1.87	1.86	0.956
SOC: Infections and infestations (10021881)	150	5.7	4.8	6.6	73	5.4	4.3	6.8	0.25	-1.31	1.70	0.741
PT: Bronchiolitis (10006448)	4	0.2	0.0	0.4	8	0.6	0.3	1.2	-0.44	-1.03	-0.08	0.016
PT: Otitis externa (10033072)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
SOC: Respiratory, thoracic and mediastinal disorders (10038738)	27	1.0	0.7	1.5	20	1.5	0.9	2.3	-0.46	-1.32	0.23	0.199
PT: Rhinorrhoea (10039101)	0	0.0	0.0	0.1	6	0.4	0.2	1.0	-0.45	-0.97	-0.20	0.001
Unsolicited AEs assessed as related to vaccination												
At least one symptom	772	29.2	27.4	30.9	373	27.7	25.3	30.1	1.51	-1.48	4.42	0.320
SOC: General disorders and administration site conditions (10018065)	598	22.6	21.0	24.2	270	20.0	17.9	22.3	2.57	-0.14	5.20	0.063
PT: Irritability (10022998)	373	14.1	12.8	15.5	147	10.9	9.3	12.7	3.19	1.01	5.28	0.005

N = number of subjects having received at least one dose of HRV vaccine/placebo

n/% = number/percentage of subjects with at least one unsolicited AE in the specified category reported within 31 days after any HRV vaccine/placebo doses

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

95% CI* = asymptotic standardized 95% confidence interval; L.L. = lower limit, U.L. = upper limit

P-value = result of the comparison between groups of the percentages of subjects with the specified unsolicited AE reported within 31 days after any doses, by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 have been used as an aid to highlight potential imbalances worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Refer to Section 9.6 for information on AEs leading to withdrawal at Visit 5.

AEs reported after intramuscular administration of HRV vaccine or placebo

[redacted] All solicited symptoms after Dose 1 were assessed by the investigator as related to vaccination. No injection site reactions were reported. Unsolicited AE, grade 1 "Drug administration error (MedDRA PT 10064295)", was noted following the wrong route of administration; the child was asymptomatic and the event was considered resolved after 3 days. [redacted] The treatment code for this subject was not broken.

9.5. Serious adverse events

Table 68 presents the percentage of subjects with SAEs/IS occurring from Dose 1 of HRV vaccine/placebo up to Visit 5.

From Dose 1 of HRV vaccine/placebo up to Visit 5,

- 5.5% (95% CI: 4.6%; 6.4%) subjects in HRV vaccine group and 7.0% (95% CI: 5.7%; 8.5%) subjects in the placebo reported at least one SAE (P-value = 0.049).
- One subject from the HRV vaccine group reported IS, assessed as related to vaccination, on Day 8 post Dose 2 of HRV vaccine (refer to Section 9.5.2 for description of this SAE). No more IS cases were reported during the follow-up period until Visit 5. No conclusions can be drawn on the basis of the single IS case observed from Dose 1 of HRV vaccine/placebo up to Visit 5.

Table 68 Percentage of subjects with SAEs/IS occurring from Dose 1 of HRV vaccine/placebo up to Visit 5 – Pooled countries (Total vaccinated cohort)

	HRV					Placebo					Risk Difference (HRV minus Placebo)			P-value
				95% CI					95% CI			95% CI*		
	N	n	%	LL	UL	N	n	%	LL	UL	%	LL	UL	
At least one SAE	2646	145	5.5	4.6	6.4	1348	95	7.0	5.7	8.5	-1.57	-3.26	-0.01	0.049
At least one IS	2646	1	0.0	0.0	0.2	1348	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

N = number of subjects having received at least one dose of HRV vaccine/placebo
n/% = number/percentage of subjects with at least one SAE/IS reported between the day of administration of dose 1 of HRV vaccine/placebo up to Visit 5 or last contact if Visit 5 not performed
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardized 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = result of the comparison between groups of percentages of subjects with the specified unsolicited AE reported within 31 days after any doses, by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 have been used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Appendix 1A presents the case narratives for SAEs occurring from Dose 1 of HRV vaccine/placebo up to Visit 5. Appendix 1B presents the summary table for SAEs occurring from Dose 1 of HRV vaccine/placebo up to Visit 5.

9.5.1. Fatal events

No fatal events were reported from Dose 1 of HRV vaccine/placebo up to Visit 5.

9.5.2. Non-fatal events

A total of 240 subjects (145 in the HRV vaccine group and 95 in the Placebo group) reported at least one non-fatal SAE from Dose 1 of HRV vaccine/placebo up to Visit 5.

[redacted] All other SAEs will remain blinded until study end.

SAEs reported by two subjects were assessed as related to vaccination. Brief description of these events is given below.

- [redacted] The events resolved after seven days and the subject was discharged. The investigator considered the event as life-threatening. The investigator considered there was reasonable possibility that the IS may have been caused by investigational product.

  [redacted] In light of results from the large phase III study rota-023 that established the safety of GSK Biologicals' HRV vaccine with respect to definite IS [Ruiz Palacios, 2006], no testing was performed on samples collected from this case (the collected samples are being stored at GSK Biologicals, Rixensart, Belgium).

- [redacted] The investigator considered there was reasonable possibility that the SAE may have been caused by investigational product. The investigator also considered the SAE to be possibly associated with viral infection.

[redacted]

9.6. Adverse Events Leading to Premature Discontinuation of Study Vaccine and/or Study

Four subjects were withdrawn at Visit 5 due to non-fatal SAEs. All SAEs leading to drop out at Visit 5 were considered by the investigators to be not related to vaccination. Supplement 366 presents a summary of SAEs leading to drop-out at Visit 5. Refer to the case narratives in Appendix 1A for complete description of the SAEs.

Nine subjects were withdrawn at Visit 5 due to non-serious AEs. The investigators assessed the non-serious AE that was reported as the reason for the drop-out as related to vaccination for 5 subjects and not assessed as related to vaccination for 4 subjects. Supplement 367 presents the non-serious AEs leading to drop-out at Visit 5.

9.7. Concomitant medications/vaccinations

Table 69 presents the number and percentage of doses and of subjects who started taking at least one concomitant medication from Day 0 to Day 7 after HRV vaccine/placebo doses by type.

- The overall percentage of subjects who started taking at least one concomitant medication from Day 0 to Day 7 after HRV vaccine/placebo doses was similar between the two groups.
- The overall percentage of subjects who received any antipyretic medication (prophylactically) from Day 0 to Day 7 after HRV vaccine/placebo doses was similarly low in both groups.
- The overall percentage of subjects who took antibiotics from Day 0 to Day 7 after HRV vaccine/placebo doses was similarly low in both groups.

Table 69 Percentage of doses and of subjects having at least one concomitant medication reported from Day 0 to Day 7 after HRV vaccine/placebo doses, by type – Pooled countries – Total vaccinated cohort

	HRV					Placebo				
				95% CI					95% CI	
Medication type	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Dose 1										
Any medication	2646	738	27.9	26.2	29.6	1348	310	23.0	20.8	25.3
Any antipyretic	2646	652	24.6	23.0	26.3	1348	277	20.5	18.4	22.8
Prophylactic antipyretic	2646	76	2.9	2.3	3.6	1348	30	2.2	1.5	3.2
Any antibiotic	2646	27	1.0	0.7	1.5	1348	12	0.9	0.5	1.5
Dose 2										
Any medication	2621	725	27.7	26.0	29.4	1338	348	26.0	23.7	28.4
Any antipyretic	2621	636	24.3	22.6	26.0	1338	310	23.2	20.9	25.5
Prophylactic antipyretic	2621	39	1.5	1.1	2.0	1338	23	1.7	1.1	2.6
Any antibiotic	2621	47	1.8	1.3	2.4	1338	20	1.5	0.9	2.3
Overall/dose										
Any medication	5267	1463	27.8	26.6	29.0	2686	658	24.5	22.9	26.2
Any antipyretic	5267	1288	24.5	23.3	25.6	2686	587	21.9	20.3	23.5
Prophylactic antipyretic	5267	115	2.2	1.8	2.6	2686	53	2.0	1.5	2.6
Any antibiotic	5267	74	1.4	1.1	1.8	2686	32	1.2	0.8	1.7
Overall/subject										
Any medication	2646	1066	40.3	38.4	42.2	1348	491	36.4	33.9	39.1
Any antipyretic	2646	929	35.1	33.3	37.0	1348	428	31.8	29.3	34.3
Prophylactic antipyretic	2646	92	3.5	2.8	4.2	1348	40	3.0	2.1	4.0
Any antibiotic	2646	71	2.7	2.1	3.4	1348	32	2.4	1.6	3.3

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

For each dose:

N = number of subjects having received the considered dose of HRV vaccine/placebo

n/% = number/percentage of HRV vaccine/placebo doses with at least one of the specified concomitant medication administration started between Day 0 and Day 7.

0 to Day 7 after the considered dose of HRV vaccine/placebo

For overall/dose:

N = total number of HRV vaccine/placebo doses administered

n/% = number/percentage of HRV vaccine/placebo doses with at least one specified concomitant medication, from Day 0 to Day 7.

For overall/subject:

N = total number of subjects having received at least one dose of HRV vaccine/placebo

n/% = total number/percentage of subject who started taking the specified concomitant medication at least once after any HRV vaccine/placebo doses, from Day 0 to Day 7

9.8. Safety conclusions

- There was no evidence for a clinically meaningful difference between the HRV vaccine group and the Placebo group for SAEs reported from Dose 1 up to Visit 5 or unsolicited AEs reported within 31 days (Day 0 to Day 30) after each dose.
- The reactogenicity profile of two doses of HRV vaccine co-administered with childhood vaccinations was similar to that of the placebo in terms of the solicited symptoms reported within eight days (Day 0 to Day 7) after each dose.

10. DISCUSSION AND CONCLUSIONS

This phase IIIb, double-blind, randomized study was conducted in Czech Republic, Finland, France, Germany, Italy and Spain to evaluate the efficacy, immunogenicity, reactogenicity and safety of two doses of HRV vaccine in healthy infants when co-administered with specific childhood vaccinations in the European setting. The immunogenicity of childhood vaccinations was also evaluated to explore any effect of co-administration with the HRV vaccine. The study design followed the childhood vaccination schedules in each country using Infanrix Hexa, Infanrix Polio Hib, Prevenar and Meningitec which represent routine vaccines currently used in Europe.

Two doses of HRV vaccine were highly effective against RV GE of any severity (VE 87.1%, P-value < 0.001) and against severe RV GE (VE 95.8%, P-value < 0.001) through one RV season. For RV GE episodes with increasing severity (Vesikari scores between 11 and 20), VE was increasingly higher, reaching 100% against more severe RV GE (Vesikari score ≥ 17 points). The HRV vaccine was also highly effective in preventing hospitalization for RV GE (VE 100%, P-value < 0.001) and reducing the need for medical attention for RV GE (VE 91.8%, P-value < 0.001). These efficacy results are similar to or better than those in previous HRV vaccine studies [Vesikari, 2004; Salinas , 2005; Ruiz Palacios, 2006], as well as RotaShield™ [Joensuu, 1997] and Rotateq™ [Vesikari, 2006] results.

The vaccine was highly effective in preventing any RV GE (VE 95.6%) and severe RV GE (VE 96.4%) caused by the homologous G1 P[8] type. Significant protection was also observed against G3, G4 and G9 types which also share the P[8] antigen. VE against G2 RV type that does not share any of the outer or inner capsid antigens of the HRV vaccine strain was 62.0% against any RV GE (P-value = 0.234) and 74.7% VE against severe RV GE (P-value = 0.263). An exploratory meta analysis of severe RV GE episodes caused by G2 type from this study and studies rota 004, 006 and 023 showed substantial protection with VE of 67.2% (95% CI, 18.8%; 88.2%) [Perez-Schael, 2005]. With regards to all isolated non-G1 types (G2, G3, G4 and G9), significant protection was shown against any RV GE (VE 79.3%, P-value < 0.001) and severe RV GE (VE 95.4%, P-value < 0.001). These results indicate that the HRV vaccine can provide good protection against the circulating RV types in the European setting. Similar efficacy against G1 and non-G1 RV types was shown in HRV vaccine studies in Latin America [Salinas , 2005; Ruiz Palacios, 2006].

In addition to using the Vesikari scale [Ruuska , 1990], the use of Clark scale [Clark, 1988] was explored to calculate the severity of GE episodes. Despite some distribution differences in the two scales, the observed VE results against severe RV GE were similar using the two scales for the purpose of this analysis.

Results of the total vaccinated cohort analysis (intent-to-treat) that included all infants with available data were fully consistent with the ATP analysis. VE from Dose 1 until end of the 1st efficacy period was 87.3% (P-value < 0.001) against any RV GE and 96.0% (P-value < 0.001) against severe RV GE.

The HRV vaccine significantly reduced the overall burden of GE of any cause during the first year of life. VE against all GE related hospitalizations was 74.7% (P-value < 0.001) and VE against severe GE was 52.3% (P-value < 0.001).

Two oral doses of the HRV vaccine were highly immunogenic with anti-rotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%), consistent with IgA results from previous HRV vaccine trials [Vesikari , 2004; Vesikari, 2004; Salinas , 2005]. Immunogenicity of HRV vaccine was good in each country, with seroconversion rates ranging between 82.1% (95% CI: 75.1%; 87.7%) and 94.6% (95% CI: 90.0%; 97.5%). The observed IgA seroconversion rate in Finland (3, 5 month schedule) seems to be higher than in the other countries. As this study was not designed to examine differences in IgA response between countries, valid conclusion can not be drawn. The differences between countries are likely due to different schedules used in different countries. Although the 3, 5 month schedule seems to yield better IgA response, early protection of RV disease is important. An analysis by feeding criteria showed breast-feeding did not appear to have an impact on anti-rotavirus IgA response and VE.

Since IgA response was evaluated only in a subset of subjects, it was difficult to draw a conclusion on correlation between seroconversion rate and VE. Previous efficacy studies of the HRV vaccine found that seroconversion rate after two doses of HRV vaccine correlated well with VE [Vesikari, 2004; Salinas , 2005].

By evaluating the co-administration of HRV vaccine with currently used childhood vaccinations given according to the primary vaccination schedules in each country, this study was able to provide key co-administration data. Co-administration of HRV vaccine with routinely used Infanrix Hexa, Infanrix Polio Hib, Prevenar or Meningitec vaccines did not appear to have any effect on the immunogenicity of any of the routine vaccine antigens. The seropositivity rates/seroprotection rates or GMCs/GMTs for antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP were similar between the HRV vaccine and Placebo groups after three doses of childhood vaccinations. Also, immunogenicity of routine vaccine antigens after two doses of childhood vaccinations was similar between the HRV vaccine and Placebo groups in Finland, Italy and Spain. Post Dose 3 response to each of the 7 *Streptococcus pneumoniae* serotypes in France and Germany, as well as the SBA-MenC and anti-PSC response in Spain were similar between the HRV vaccine and Placebo groups. Likewise, co-administration of HRV vaccine with the childhood vaccines did not have any effect on the reactogenicity profile. Overall, no interference was found when HRV vaccine was co-administered with childhood vaccinations. Previous studies found no immune interference between HRV vaccine and childhood vaccinations used in the USA and Canada [Dennehy, 2005], and in Latin America [Salinas , 2005].

A high level of seroprotection rate /seropositivity rate to each childhood vaccine antigen was observed for both groups at post Dose 3 of childhood vaccines in each country, except for lower response in both groups in Germany. Investigations into reasons for the lower response in Germany indicated that the lower response may have been due to center-specific issues at one particular center (Center [redacted] Post-hoc analysis indicated that the immune response at Center [redacted] was much lower and investigations at this center are ongoing to fully understand the observations. Exclusion of Center [redacted] from

analysis for Germany resulted in immune response that was similar to other countries. The commercial Infanrix Hexa lot used in Center [redacted] was also used at other centers in Germany and in some centers in Czech Republic. Since low immune response was observed only in Center [redacted] it appears to be a center-specific issue and any concerns on immunogenicity of Infanrix Hexa can be ruled out.

As observed in previous HRV vaccine trials [Vesikari , 2004; Vesikari, 2004; Salinas , 2005; Dennehy, 2005], the reactogenicity profile of the HRV vaccine was similar to the placebo. The overall reactogenicity profile of the HRV vaccine was very mild with no increase in any solicited symptoms including fever, diarrhea and vomiting as compared with the placebo during eight days after each dose. Overall percentages of subjects with unsolicited AEs and SAEs reported from Dose 1 up to Visit 5 were similar between the HRV vaccine and Placebo groups. Potential imbalances in unsolicited AEs noted between the groups were not clinically meaningful. A phase III trial involving more than 60,000 infants has proved that the HRV vaccine is not associated with an increased risk of IS as compared to placebo [Ruiz Palacios, 2006]. Within the present trial setting, the vaccine was not associated with an increased risk of IS from Dose 1 up to Visit 5 compared to the placebo; the observed Risk Difference was 0.04% (95% CI: -0.25%; 0.21%, P-value = 0.457).

Overall, the excellent protection against RV GE hospitalizations, any and severe RV GE due to G1 and non-G1 RV and the important reduction of severe cases and hospitalization for GE of any cause indicate that two doses of the HRV vaccine would provide significant public health value when integrated in routine infant immunization schedules.

Overall conclusions

Efficacy

- Two oral doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccinations were highly effective compared to the placebo in protecting infants against any RV GE caused by the circulating wild-type RV during the first efficacy period. VE against any RV GE was 87.1% (95% CI: 79.6%; 92.1%). The primary objective of this study was met.
- Two oral doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccinations were highly effective during the first efficacy period compared to the placebo in protecting infants against:
  - Severe RV GE caused by the circulating wild-type RV; VE 95.8% (95% CI: 89.6%; 98.7%)
  - Any RV GE caused by G1 wild-type RV; VE 95.6% (95% CI: 87.9%; 98.8%)
  - Severe RV GE caused by G1 wild-type RVs; VE 96.4% (95% CI: 85.7%; 99.6%)
  - Any RV GE caused by non-G1 RV types; VE 79.3% (95% CI: 64.6%; 88.4%)
  - Severe RV GE caused by non-G1 RV types; VE 95.4% (95% CI: 85.3%; 99.1%)

  - Hospitalization due to RV GE caused by the circulating wild-type RV; VE 100% (95% CI: 81.8%; 100%)
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention; 91.8% (95% CI: 84.0%; 96.3%)

- Already after the first dose, GSK Biologicals' HRV vaccine was protective against any and severe RV GE caused by the circulating wild-type RV. VE against any RV GE was 89.8% (95% CI: 8.9%; 99.8%) during the period from Dose 1 to before Dose 2. VE estimates for the period from Dose 1 until Visit 5 were consistent with estimates for the first efficacy period.

Immunogenicity

- GSK Biologicals' HRV vaccine was immunogenic as shown by the anti-rotavirus IgA antibody seroconversion rate of 86.5% (95% CI: 83.9%; 88.8%) observed in the HRV vaccine group at one to two months after Dose 2.
- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of any antigens contained in each of the co-administered childhood vaccinations (Infanrix Hexa, Infanrix Polio Hib, Prevenar or Meningitec).

Safety

- There was no evidence for a clinically meaningful difference between the HRV vaccine group and the Placebo group for SAEs reported from Dose 1 up to Visit 5 or unsolicited AEs reported within 31 days (Day 0 to Day 30) after each dose.
- The reactogenicity profile of two doses of HRV vaccine co-administered with childhood vaccinations was similar to that of the placebo in terms of the solicited symptoms reported within eight days (Day 0 to Day 7) after each dose.

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13. APPENDICES

List of Appendices available for the study report

Clintrial Eligibility Codes

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Appendix 1A Narratives for Serious Adverse Events reported from Dose 1 to Visit 5
Appendix 1B Serious Adverse Events Summary Table for SAEs reported from Dose 1 to Visit 5

APPENDIX 2: STUDY INFORMATION
Appendix 2A Protocol and protocol amendments
Appendix 2B Sample Case Report form (unique pages only)
Appendix 2C List of IECs or IRBs
Appendix 2D Representative Written information for patient and sample consent forms
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Appendix 2F Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
Appendix 2G Signature of principal or coordinating investigator
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Appendix 2J Publications based on the study
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Clintrial Eligibility Codes

Elimination from ATP cohorts for reactogenicity, immunogenicity and efficacy

1010 Subject or vaccine number not allocated
No subject allocated to the randomized number
1030 Study vaccine dose not administered AT ALL but subject number allocated
1040 Administration of intercurrent vaccine(s) forbidden in the protocol
1060 Randomization code broken
1070 Study vaccine dose not administered according to protocol :
- Replacement/ Wrong vaccine vial used NOT corresponding to the correct randomization group
- Subject number not in the randomization list and not requested by the sponsor (extra PID)
1500 Initially seropositive or initially unknown anti-rotavirus IgA antibody status on the day of Dose 1 of HRV vaccine or placebo for subjects included in the immunogenicity and reactogenicity subset.

Elimination from ATP cohort for reactogenicity and from ATP cohort for immunogenicity

1035 Subjects for whom solicited symptoms were not to be collected and who were not planned to be bled for all blood sampling visits

Elimination from ATP cohort for immunogenicity

2010 Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.
2040 Administration of any intercurrent medication forbidden by the protocol
2050 Underlying medical condition forbidden by the protocol
2060 Concomitant infection by rotavirus which may influence immune response (=rotavirus other than vaccine strain in GE stool samples collected up to Visit 3)
2070 Concomitant infection not related to the vaccine which may influence immune response
2080 Non compliance with vaccination schedules for HRV vaccine or placebo (dates of vaccination not corresponding to adapted protocol intervals or unknown vaccination dates)
2090 Non compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS dates)
2100 Serological results not available for the blood sample POST vaccination (including BS lost, Not Done, unable to test, absence of parallelism):
2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between eCRF and results, wrong labelling in BS)

Important remark: if code 2100 was attributed to a subject, codes 2080 and/or 2090 were not to be assigned to the same subject

Elimination from ATP cohort for efficacy – first efficacy period

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 other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response

LIST OF SUPPLEMENTS

PAGE

Supplement 1 Number of subjects enrolled in each center, by group – Total vaccinated cohort

	HRV N = 2646		Placebo N = 1348		Total N = 3994	
Center	n	%	n	%	n	%
Czech Republic						
[redacted]	8	0.3	4	0.3	12	0.3
	16	0.6	8	0.6	24	0.6
	8	0.3	4	0.3	12	0.3
	40	1.5	20	1.5	60	1.5
	36	1.4	18	1.3	54	1.4
	20	0.8	10	0.7	30	0.8
	3	0.1	2	0.1	5	0.1
	8	0.3	4	0.3	12	0.3
	20	0.8	10	0.7	30	0.8
	16	0.6	8	0.6	24	0.6
	8	0.3	4	0.3	12	0.3
	8	0.3	4	0.3	12	0.3
	8	0.3	4	0.3	12	0.3
Finland						
[redacted]	199	7.5	97	7.2	296	7.4
	194	7.3	99	7.3	293	7.3
	87	3.3	43	3.2	130	3.3
	93	3.5	46	3.4	139	3.5
	146	5.5	74	5.5	220	5.5
	125	4.7	64	4.7	189	4.7
	46	1.7	24	1.8	70	1.8
	94	3.6	49	3.6	143	3.6
	32	1.2	17	1.3	49	1.2
	35	1.3	17	1.3	52	1.3
	82	3.1	41	3.0	123	3.1
	92	3.5	47	3.5	139	3.5
	81	3.1	39	2.9	120	3.0
	172	6.5	88	6.5	260	6.5
	66	2.5	30	2.2	96	2.4
	90	3.4	46	3.4	136	3.4
	59	2.2	31	2.3	90	2.3
	43	1.6	24	1.8	67	1.7
	69	2.6	35	2.6	104	2.6
	49	1.9	25	1.9	74	1.9
	64	2.4	36	2.7	100	2.5
France						
[redacted]	6	0.2	4	0.3	10	0.3
	3	0.1	1	0.1	4	0.1
	1	0.0	0	0.0	1	0.0
	3	0.1	1	0.1	4	0.1
	5	0.2	2	0.1	7	0.2
	4	0.2	2	0.1	6	0.2
	6	0.2	3	0.2	9	0.2
	14	0.5	8	0.6	22	0.6
	27	1.0	14	1.0	41	1.0
	8	0.3	5	0.4	13	0.3
	1	0.0	1	0.1	2	0.1
	7	0.3	3	0.2	10	0.3
	1	0.0	0	0.0	1	0.0

	HRV N = 2646		Placebo N = 1348		Total N = 3994	
Center	**n**	**%**	**n**	**%**	**n**	**%**
[redacted]	1	0.0	0	0.0	1	0.0
	1	0.0	1	0.1	2	0.1
	1	0.0	1	0.1	2	0.1
	1	0.0	1	0.1	2	0.1
	1	0.0	1	0.1	2	0.1
	3	0.1	1	0.1	4	0.1
	1	0.0	2	0.1	3	0.1
Germany						
[redacted]	16	0.6	8	0.6	24	0.6
	2	0.1	1	0.1	3	0.1
	40	1.5	20	1.5	60	1.5
	8	0.3	3	0.2	11	0.3
	11	0.4	6	0.4	17	0.4
	4	0.2	2	0.1	6	0.2
	2	0.1	1	0.1	3	0.1
	3	0.1	2	0.1	5	0.1
	2	0.1	1	0.1	3	0.1
	4	0.2	2	0.1	6	0.2
	7	0.3	4	0.3	11	0.3
	3	0.1	2	0.1	5	0.1
	2	0.1	0	0.0	2	0.1
	1	0.0	1	0.1	2	0.1
	2	0.1	2	0.1	4	0.1
	2	0.1	1	0.1	3	0.1
	8	0.3	4	0.3	12	0.3
	8	0.3	4	0.3	12	0.3
	4	0.2	2	0.1	6	0.2
	4	0.2	3	0.2	7	0.2
	20	0.8	10	0.7	30	0.8
	3	0.1	2	0.1	5	0.1
	16	0.6	8	0.6	24	0.6
	4	0.2	2	0.1	6	0.2
	4	0.2	2	0.1	6	0.2
	10	0.4	6	0.4	16	0.4
Italy						
[redacted]	7	0.3	5	0.4	12	0.3
	8	0.3	5	0.4	13	0.3
Spain						
[redacted]	6	0.2	3	0.2	9	0.2
	99	3.7	50	3.7	149	3.7
	16	0.6	8	0.6	24	0.6
	60	2.3	31	2.3	91	2.3
	3	0.1	1	0.1	4	0.1
	6	0.2	3	0.2	9	0.2
	8	0.3	4	0.3	12	0.3
	6	0.2	3	0.2	9	0.2
	3	0.1	2	0.1	5	0.1
	10	0.4	5	0.4	15	0.4
	5	0.2	3	0.2	8	0.2
	3	0.1	1	0.1	4	0.1
	4	0.2	2	0.1	6	0.2

N = number of subjects enrolled in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects enrolled in a given center

Supplement 2 Summary of feeding criteria at Dose 1 and Dose 2 of HRV/Placebo, by country and for pooled countries – ATP cohort for efficacy

		HRV N = 2572		Placebo N = 1302		Total N = 3874	
Country	**Infant was breast fed at**	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	**Both doses**	157	81.3	73	75.3	230	79.3
	One dose	9	4.7	7	7.2	16	5.5
	None	27	14.0	17	17.5	44	15.2
Finland	**Both doses**	1306	69.0	674	70.5	1980	69.5
	One dose	219	11.6	116	12.1	335	11.8
	None	368	19.4	166	17.4	534	18.7
France	**Both doses**	30	31.6	16	32.0	46	31.7
	One dose	12	12.6	15	30.0	27	18.6
	None	53	55.8	19	38.0	72	49.7
Germany	**Both doses**	98	54.7	53	56.4	151	55.3
	One dose	30	16.8	11	11.7	41	15.0
	None	51	28.5	30	31.9	81	29.7
Italy	**Both doses**	8	53.3	6	60.0	14	56.0
	One dose	2	13.3	1	10.0	3	12.0
	None	5	33.3	3	30.0	8	32.0
Spain	**Both doses**	88	44.7	47	49.5	135	46.2
	One dose	46	23.4	22	23.2	68	23.3
	None	63	32.0	26	27.4	89	30.5
Pooled countries	**Both doses**	1687	65.6	869	66.7	2556	66.0
	One dose	318	12.4	172	13.2	490	12.6
	None	567	22.0	261	20.0	828	21.4

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category, by country and for pooled countries

Supplement 3 Percentage of subjects vaccinated before the RV season - ATP cohort for efficacy

		HRV		Placebo	
		N= 2572		N= 1302	
Country	**Vaccinated before the RV season**	**n**	**%**	**n**	**%**
Czech Republic	**Yes**	94	48.7	46	47.4
	No	99	51.3	51	52.6
Finland	**Yes**	120	6.3	62	6.5
	No	1773	93.7	894	93.5
France	**Yes**	11	11.6	8	16.0
	No	84	88.4	42	84.0
Germany	**Yes**	16	8.9	11	11.7
	No	163	91.1	83	88.3
Italy	**Yes**	0	0.0	0	0.0
	No	15	100	10	100
Spain	**Yes**	0	0.0	0	0.0
	No	197	100	95	100
All countries	**Yes**	241	9.4	127	9.8
	No	2331	90.6	1175	90.2

n/% = number/percentage of subjects in the specified category

Supplement 4 Summary of demographic characteristics – Pooled countries – Total vaccinated cohort

		HRV N = 2646		Placebo N = 1348		Total N = 3994	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	11.5	-	11.4	-	11.5	-
	SD	1.81	-	1.84	-	1.82	-
	Minimum	5	-	6	-	5	-
	Median	12.0	-	12.0	-	12.0	-
	Maximum	18	-	16	-	18	-
Age at Dose 2 (weeks)	**Mean**	19.6	-	19.6	-	19.6	-
	SD	2.70	-	2.74	-	2.71	-
	Minimum	10	-	10	-	10	-
	Median	20.0	-	20.0	-	20.0	-
	Maximum	30	-	27	-	30	-
	Unknown	25	-	10	-	35	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	10.2	-	10.3	-	10.3	-
	SD	1.58	-	1.55	-	1.57	-
	Minimum	2	-	2	-	2	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	13	-	13	-	13	-
Gender	**Female**	1230	46.5	657	48.7	1887	47.2
	Male	1416	53.5	691	51.3	2107	52.8
Race	**African heritage**	6	0.2	5	0.4	11	0.3
	White/Caucasian	2604	98.4	1323	98.1	3927	98.3
	Arabic/north African	9	0.3	3	0.2	12	0.3
	East/south east Asian	1	0.0	1	0.1	2	0.1
	South Asian	4	0.2	1	0.1	5	0.1
	American Hispanic	13	0.5	6	0.4	19	0.5
	Japanese	0	0.0	0	0.0	0	0.0
	Other	9	0.3	9	0.7	18	0.5
Height (cm)	**Mean**	60.4	-	60.4	-	60.4	-
	SD	2.95	-	2.95	-	2.95	-
	Median	61.0	-	61.0	-	61.0	-
	Unknown	2	-	3	-	5	-
Weight (kg)	**Mean**	6.0	-	6.0	-	6.0	-
	SD	0.86	-	0.84	-	0.86	-
	Median	6.0	-	6.0	-	6.0	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	**Mean**	16.4	-	16.3	-	16.4	-
	SD	1.52	-	1.54	-	1.52	-
	Median	16.3	-	16.3	-	16.3	-
	Unknown	2	-	3	-	5	-

N = number of subjects in the considered group or in total (sum of both 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 - Czech Republic – Total vaccinated cohort

		HRV N = 199		Placebo N = 100		Total N = 299	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	12.2	-	12.2	-	12.2	-
	SD	1.52	-	1.51	-	1.52	-
	Minimum	9	-	9	-	9	-
	Median	12.0	-	12.0	-	12.0	-
	Maximum	18	-	15	-	18	-
Age at Dose 2 (weeks)	**Mean**	17.2	-	17.3	-	17.2	-
	SD	1.64	-	1.68	-	1.65	-
	Minimum	13	-	13	-	13	-
	Median	17.0	-	18.0	-	17.0	-
	Maximum	23	-	23	-	23	-
	Unknown	1	-	0	-	1	-
Age at visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	10.8	-	10.8	-	10.8	-
	SD	1.27	-	1.12	-	1.22	-
	Minimum	2	-	7	-	2	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	13	-	12	-	13	-
Gender	**Female**	93	46.7	48	48.0	141	47.2
	Male	106	53.3	52	52.0	158	52.8
Race	**African heritage**	0	0.0	0	0.0	0	0.0
	White/Caucasian	198	99.5	100	100.0	298	99.7
	Arabic/north African	0	0.0	0	0.0	0	0.0
	East/south east Asian	0	0.0	0	0.0	0	0.0
	South Asian	0	0.0	0	0.0	0	0.0
	American Hispanic	0	0.0	0	0.0	0	0.0
	Japanese	0	0.0	0	0.0	0	0.0
	Other	1	0.5	0	0.0	1	0.3
Height (cm)	**Mean**	60.6	-	60.7	-	60.6	-
	SD	3.09	-	3.13	-	3.10	-
	Median	60.0	-	61.0	-	60.0	-
Weight (kg)	**Mean**	5.9	-	5.8	-	5.9	-
	SD	0.76	-	0.82	-	0.78	-
	Median	5.8	-	5.8	-	5.8	-
BMI (kg/m²)	**Mean**	16.1	-	15.8	-	16.0	-
	SD	1.90	-	2.20	-	2.01	-
	Median	15.9	-	15.6	-	15.8	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 6 Summary of demographic characteristics – Finland – Total vaccinated cohort

		HRV N = 1918		Placebo N = 972		Total N = 2890	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	12.1	-	12.1	-	12.1	-
	SD	0.91	-	0.92	-	0.91	-
	Minimum	9	-	9	-	9	-
	Median	12.0	-	12.0	-	12.0	-
	Maximum	14	-	15	-	15	-
Age at Dose 2 (weeks)	**Mean**	20.9	-	20.9	-	20.9	-
	SD	1.41	-	1.41	-	1.41	-
	Minimum	17	-	18	-	17	-
	Median	21.0	-	21.0	-	21.0	-
	Maximum	29	-	27	-	29	-
	Unknown	18	-	7	-	25	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	10.7	-	10.8	-	10.8	-
	SD	1.07	-	1.00	-	1.04	-
	Minimum	3	-	5	-	3	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	13	-	13	-	13	-
Gender	**Female**	885	46.1	482	49.6	1367	47.3
	Male	1033	53.9	490	50.4	1523	52.7
Race	**African heritage**	3	0.2	1	0.1	4	0.1
	White/Caucasian	1909	99.5	962	99.0	2871	99.3
	Arabic/north African	0	0.0	1	0.1	1	0.0
	East/south east Asian	0	0.0	0	0.0	0	0.0
	South Asian	0	0.0	0	0.0	0	0.0
	American Hispanic	0	0.0	1	0.1	1	0.0
	Japanese	0	0.0	0	0.0	0	0.0
	Other	6	0.3	7	0.7	13	0.4
Height (cm)	**Mean**	61.2	-	61.2	-	61.2	-
	SD	2.27	-	2.27	-	2.27	-
	Median	61.0	-	61.0	-	61.0	-
	Unknown	2	-	1	-	3	-
Weight (kg)	**Mean**	6.2	-	6.2	-	6.2	-
	SD	0.75	-	0.73	-	0.74	-
	Median	6.2	-	6.1	-	6.2	-
BMI (kg/m²)	**Mean**	16.6	-	16.5	-	16.6	-
	SD	1.43	-	1.42	-	1.43	-
	Median	16.5	-	16.4	-	16.4	-
	Unknown	2	-	1	-	3	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 7 Summary of demographic characteristics - France – Total vaccinated cohort

		HRV N = 95		Placebo N = 51		Total N = 146	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	9.1	-	9.3	-	9.2	-
	SD	1.57	-	1.72	-	1.62	-
	Minimum	6	-	6	-	6	-
	Median	9.0	-	9.0	-	9.0	-
	Maximum	14	-	15	-	15	-
Age at Dose 2 (weeks)	**Mean**	14.0	-	14.3	-	14.1	-
	SD	1.70	-	2.00	-	1.81	-
	Minimum	11	-	10	-	10	-
	Median	14.0	-	14.0	-	14.0	-
	Maximum	20	-	21	-	21	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	8.7	-	8.8	-	8.8	-
	SD	1.64	-	1.83	-	1.70	-
	Minimum	3	-	3	-	3	-
	Median	9.0	-	9.0	-	9.0	-
	Maximum	12	-	12	-	12	-
Gender	**Female**	40	42.1	34	66.7	74	50.7
	Male	55	57.9	17	33.3	72	49.3
Race	**African heritage**	2	2.1	1	2.0	3	2.1
	White/Caucasian	89	93.7	47	92.2	136	93.2
	Arabic/north African	2	2.1	1	2.0	3	2.1
	East/south east Asian	0	0.0	0	0.0	0	0.0
	South Asian	1	1.1	0	0.0	1	0.7
	American Hispanic	0	0.0	0	0.0	0	0.0
	Japanese	0	0.0	0	0.0	0	0.0
	Other	1	1.1	2	3.9	3	2.1
Height (cm)	**Mean**	57.3	-	57.0	-	57.2	-
	SD	3.11	-	3.12	-	3.10	-
	Median	58.0	-	58.0	-	58.0	-
Weight (kg)	**Mean**	5.1	-	5.2	-	5.2	-
	SD	0.79	-	0.81	-	0.80	-
	Median	5.1	-	5.3	-	5.2	-
BMI (kg/m²)	**Mean**	15.6	-	16.0	-	15.7	-
	SD	1.47	-	1.65	-	1.54	-
	Median	15.5	-	15.9	-	15.6	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 8 Summary of demographic characteristics - Germany – Total vaccinated cohort

		HRV N = 190		Placebo N = 99		Total N = 289	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	10.4	-	10.0	-	10.3	-
	SD	2.17	-	2.22	-	2.19	-
	Minimum	5	-	6	-	5	-
	Median	10.0	-	10.0	-	10.0	-
	Maximum	15	-	16	-	16	-
Age at Dose 2 (weeks)	**Mean**	15.6	-	15.3	-	15.5	-
	SD	2.51	-	2.66	-	2.56	-
	Minimum	10	-	10	-	10	-
	Median	15.0	-	15.0	-	15.0	-
	Maximum	23	-	22	-	23	-
	Unknown	3	-	0	-	3	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	9.0	-	9.2	-	9.0	-
	SD	1.91	-	1.62	-	1.82	-
	Minimum	3	-	6	-	3	-
	Median	9.0	-	9.0	-	9.0	-
	Maximum	12	-	13	-	13	-
Gender	**Female**	96	50.5	43	43.4	139	48.1
	Male	94	49.5	56	56.6	150	51.9
Race	**African heritage**	1	0.5	2	2.0	3	1.0
	White/Caucasian	180	94.7	94	94.9	274	94.8
	Arabic/north African	4	2.1	1	1.0	5	1.7
	East/south east Asian	1	0.5	1	1.0	2	0.7
	South Asian	3	1.6	1	1.0	4	1.4
	American Hispanic	0	0.0	0	0.0	0	0.0
	Japanese	0	0.0	0	0.0	0	0.0
	Other	1	0.5	0	0.0	1	0.3
Height (cm)	**Mean**	59.3	-	58.9	-	59.1	-
	SD	3.14	-	3.18	-	3.15	-
	Median	59.0	-	58.5	-	59.0	-
	Unknown	0	-	1	-	1	-
Weight (kg)	**Mean**	5.7	-	5.6	-	5.7	-
	SD	0.87	-	0.90	-	0.88	-
	Median	5.6	-	5.6	-	5.6	-
BMI (kg/m²)	**Mean**	16.2	-	16.0	-	16.1	-
	SD	1.43	-	1.62	-	1.49	-
	Median	16.1	-	16.2	-	16.1	-
	Unknown	0	-	1	-	1	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 9 Summary of demographic characteristics - Italy – Total vaccinated cohort

		HRV N = 15		Placebo N = 10		Total N = 25	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	11.4	-	11.0	-	11.2	-
	SD	2.20	-	1.94	-	2.07	-
	Minimum	7	-	8	-	7	-
	Median	12.0	-	11.5	-	12.0	-
	Maximum	15	-	14	-	15	-
Age at Dose 2 (weeks)	**Mean**	20.9	-	19.9	-	20.5	-
	SD	3.24	-	1.91	-	2.79	-
	Minimum	16	-	17	-	16	-
	Median	21.0	-	20.0	-	21.0	-
	Maximum	30	-	23	-	30	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	9.1	-	8.8	-	9.0	-
	SD	1.28	-	1.55	-	1.37	-
	Minimum	7	-	7	-	7	-
	Median	10.0	-	9.0	-	10.0	-
	Maximum	11	-	11	-	11	-
Gender	**Female**	4	26.7	4	40.0	8	32.0
	Male	11	73.3	6	60.0	17	68.0
Race	**African heritage**	0	0.0	1	10.0	1	4.0
	White/Caucasian	14	93.3	9	90.0	23	92.0
	Arabic/north African	0	0.0	0	0.0	0	0.0
	East/south east Asian	0	0.0	0	0.0	0	0.0
	South Asian	0	0.0	0	0.0	0	0.0
	American Hispanic	1	6.7	0	0.0	1	4.0
	Japanese	0	0.0	0	0.0	0	0.0
	Other	0	0.0	0	0.0	0	0.0
Height (cm)	**Mean**	59.5	-	59.0	-	59.3	-
	SD	4.05	-	2.49	-	3.46	-
	Median	60.0	-	60.0	-	60.0	-
Weight (kg)	**Mean**	5.4	-	5.6	-	5.5	-
	SD	0.44	-	0.59	-	0.51	-
	Median	5.4	-	5.8	-	5.5	-
BMI (kg/m²)	**Mean**	15.4	-	16.2	-	15.7	-
	SD	2.02	-	1.12	-	1.73	-
	Median	14.8	-	16.1	-	15.6	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 10 Summary of demographic characteristics – Spain – Total vaccinated cohort

		HRV N = 229		Placebo N = 116		Total N = 345	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	7.6	-	7.6	-	7.6	-
	SD	1.45	-	1.51	-	1.47	-
	Minimum	6	-	6	-	6	-
	Median	7.0	-	7.5	-	7.0	-
	Maximum	13	-	14	-	14	-
Age at Dose 2 (weeks)	**Mean**	16.6	-	16.5	-	16.6	-
	SD	1.72	-	1.72	-	1.72	-
	Minimum	13	-	13	-	13	-
	Median	17.0	-	17.0	-	17.0	-
	Maximum	24	-	25	-	25	-
	Unknown	3	-	3	-	6	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	7.4	-	7.4	-	7.4	-
	SD	0.94	-	1.15	-	1.01	-
	Minimum	2	-	2	-	2	-
	Median	7.0	-	7.0	-	7.0	-
	Maximum	10	-	10	-	10	-
Gender	**Female**	112	48.9	46	39.7	158	45.8
	Male	117	51.1	70	60.3	187	54.2
Race	**African heritage**	0	0.0	0	0.0	0	0.0
	White/Caucasian	214	93.4	111	95.7	325	94.2
	Arabic/north African	3	1.3	0	0.0	3	0.9
	East/south east Asian	0	0.0	0	0.0	0	0.0
	South Asian	0	0.0	0	0.0	0	0.0
	American Hispanic	12	5.2	5	4.3	17	4.9
	Japanese	0	0.0	0	0.0	0	0.0
	Other	0	0.0	0	0.0	0	0.0
Height (cm)	**Mean**	56.0	-	56.2	-	56.1	-
	SD	2.34	-	2.48	-	2.38	-
	Median	56.0	-	56.0	-	56.0	-
	Unknown	0	-	1	-	1	-
Weight (kg)	**Mean**	4.9	-	5.0	-	4.9	-
	SD	0.61	-	0.69	-	0.64	-
	Median	4.9	-	5.0	-	4.9	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	**Mean**	15.5	-	15.7	-	15.6	-
	SD	1.36	-	1.41	-	1.38	-
	Median	15.5	-	15.8	-	15.5	-
	Unknown	0	-	1	-	1	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 11 Summary of epidemiological data, by country and for pooled countries – Total vaccinated cohort

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	**Characteristics**	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	**Number of siblings**	**0**	97	48.7	55	55.0	152	50.8
		1	76	38.2	34	34.0	110	36.8
		2	19	9.5	10	10.0	29	9.7
		3	6	3.0	1	1.0	7	2.3
		6	1	0.5	0	0.0	1	0.3
	Day care at Visit 1	**No**	198	99.5	100	100	298	99.7
		Yes	1	0.5	0	0.0	1	0.3
	Day care at Visit 2	**No**	198	99.5	100	100	298	99.7
		Yes	0	0.0	0	0.0	0	0.0
		Missing	1	0.5	0	0.0	1	0.3
	Day care at Visit 3	**No**	196	98.5	99	99.0	295	98.7
		Yes	2	1.0	1	1.0	3	1.0
		Missing	1	0.5	0	0.0	1	0.3
	Day care at Visit 5	**No**	195	98.0	96	96.0	291	97.3
		Yes	3	1.5	3	3.0	6	2.0
		Missing	1	0.5	1	1.0	2	0.7
Finland	**Number of siblings**	**0**	940	49.0	513	52.8	1453	50.3
		1	596	31.1	283	29.1	879	30.4
		2	260	13.6	121	12.4	381	13.2
		3	92	4.8	35	3.6	127	4.4
		4	21	1.1	13	1.3	34	1.2
		5	5	0.3	4	0.4	9	0.3
		6	2	0.1	0	0.0	2	0.1
		7	2	0.1	2	0.2	4	0.1
		8	0	0.0	1	0.1	1	0.0
	Day care at Visit 1	**No**	1916	99.9	971	99.9	2887	99.9
		Yes	2	0.1	1	0.1	3	0.1
	Day care at Visit 2	**No**	1908	99.5	970	99.8	2878	99.6
		Yes	2	0.1	0	0.0	2	0.1
		Missing	8	0.4	2	0.2	10	0.3
	Day care at Visit 3	**No**	1895	98.8	964	99.2	2859	98.9
		Yes	5	0.3	1	0.1	6	0.2
		Missing	18	0.9	7	0.7	25	0.9
	Day care at Visit 5	**No**	1813	94.5	923	95.0	2736	94.7
		Yes	91	4.7	39	4.0	130	4.5
		Missing	14	0.7	10	1.0	24	0.8

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	**Characteristics**	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
France	**Number of siblings**	**0**	30	31.6	13	25.5	43	29.5
		1	48	50.5	28	54.9	76	52.1
		2	10	10.5	6	11.8	16	11.0
		3	5	5.3	2	3.9	7	4.8
		4	1	1.1	0	0.0	1	0.7
		5	1	1.1	1	2.0	2	1.4
		7	0	0.0	1	2.0	1	0.7
	Day care at Visit 1	**No**	94	98.9	47	92.2	141	96.6
		Yes	1	1.1	4	7.8	5	3.4
	Day care at Visit 2	**No**	90	94.7	46	90.2	136	93.2
		Yes	5	5.3	5	9.8	10	6.8
	Day care at Visit 3	**No**	82	86.3	45	88.2	127	87.0
		Yes	11	11.6	5	9.8	16	11.0
		Missing	2	2.1	1	2.0	3	2.1
	Day care at Visit 5	**No**	73	76.8	44	86.3	117	80.1
		Yes	20	21.1	6	11.8	26	17.8
		Missing	2	2.1	1	2.0	3	2.1
Germany	**Number of siblings**	**0**	78	41.1	38	38.4	116	40.1
		1	70	36.8	36	36.4	106	36.7
		2	26	13.7	13	13.1	39	13.5
		3	9	4.7	7	7.1	16	5.5
		4	4	2.1	3	3.0	7	2.4
		5	1	0.5	1	1.0	2	0.7
		6	1	0.5	1	1.0	2	0.7
		7	1	0.5	0	0.0	1	0.3
	Day care at Visit 1	**No**	187	98.4	98	99.0	285	98.6
		Yes	3	1.6	1	1.0	4	1.4
	Day care at Visit 2	**No**	187	98.4	99	100	286	99.0
		Yes	0	0.0	0	0.0	0	0.0
		Missing	3	1.6	0	0.0	3	1.0
	Day care at Visit 3	**No**	178	93.7	96	97.0	274	94.8
		Yes	5	2.6	3	3.0	8	2.8
		Missing	7	3.7	0	0.0	7	2.4
	Day care at Visit 5	**No**	177	93.2	97	98.0	274	94.8
		Yes	2	1.1	0	0.0	2	0.7
		Missing	11	5.8	2	2.0	13	4.5
Italy	**Number of siblings**	**0**	7	46.7	2	20.0	9	36.0
		1	8	53.3	7	70.0	15	60.0
		2	0	0.0	1	10.0	1	4.0
	Day care at Visit 1	**No**	13	86.7	9	90.0	22	88.0
		Yes	2	13.3	1	10.0	3	12.0
	Day care at Visit 2	**No**	14	93.3	10	100	24	96.0
		Yes	1	6.7	0	0.0	1	4.0
	Day care at Visit 3	**No**	15	100	10	100	25	100
		Yes	0	0.0	0	0.0	0	0.0
	Day care at Visit 5	**No**	13	86.7	10	100	23	92.0
		Yes	1	6.7	0	0.0	1	4.0
		Missing	1	6.7	0	0.0	1	4.0

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	**Characteristics**	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Spain	**Number of siblings**	**0**	137	59.8	70	60.3	207	60.0
		1	79	34.5	44	37.9	123	35.7
		2	9	3.9	1	0.9	10	2.9
		3	2	0.9	1	0.9	3	0.9
		4	2	0.9	0	0.0	2	0.6
	Day care at Visit 1	**No**	229	100	115	99.1	344	99.7
		Yes	0	0.0	1	0.9	1	0.3
	Day care at Visit 2	**No**	220	96.1	110	94.8	330	95.7
		Yes	6	2.6	3	2.6	9	2.6
		Missing	3	1.3	3	2.6	6	1.7
	Day care at Visit 3	**No**	217	94.8	107	92.2	324	93.9
		Yes	8	3.5	6	5.2	14	4.1
		Missing	4	1.7	3	2.6	7	2.0
	Day care at Visit 4	**No**	215	93.9	107	92.2	322	93.3
		Yes	10	4.4	6	5.2	16	4.6
		Missing	4	1.7	3	2.6	7	2.0
	Day care at Visit 5	**No**	214	93.4	106	91.4	320	92.8
		Yes	11	4.8	7	6.0	18	5.2
		Missing	4	1.7	3	2.6	7	2.0
Pooled countries	**Number of siblings**	**0**	1289	48.7	691	51.3	1980	49.6
		1	877	33.1	432	32.0	1309	32.8
		2	324	12.2	152	11.3	476	11.9
		3	114	4.3	46	3.4	160	4.0
		4	28	1.1	16	1.2	44	1.1
		5	7	0.3	6	0.4	13	0.3
		6	4	0.2	1	0.1	5	0.1
		7	3	0.1	3	0.2	6	0.2
		8	0	0.0	1	0.1	1	0.0
	Day care at Visit 1	**No**	2637	99.7	1340	99.4	3977	99.6
		Yes	9	0.3	8	0.6	17	0.4
	Day care at Visit 2	**No**	2617	98.9	1335	99.0	3952	98.9
		Yes	14	0.5	8	0.6	22	0.6
		Missing	15	0.6	5	0.4	20	0.5
	Day care at Visit 3	**No**	2583	97.6	1321	98.0	3904	97.7
		Yes	31	1.2	16	1.2	47	1.2
		Missing	32	1.2	11	0.8	43	1.1
	Day care at Visit 5	**No**	2485	93.9	1276	94.7	3761	94.2
		Yes	128	4.8	55	4.1	183	4.6
		Missing	33	1.2	17	1.3	50	1.3

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category, by country or for pooled countries
As Visit 4 was scheduled for Spain only, 'Day care at Visit 4' information has been collected and is presented for that country only.

Supplement 12 Summary of demographic characteristics – Pooled countries –Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV N = 914		Placebo N = 490		Total N = 1404	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	10.4	-	10.4	-	10.4	-
	SD	2.48	-	2.46	-	2.47	-
	Minimum	5	-	6	-	5	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	18	-	16	-	18	-
Age at Dose 2 (weeks)	**Mean**	17.3	-	17.4	-	17.3	-
	SD	2.94	-	3.02	-	2.97	-
	Minimum	10	-	10	-	10	-
	Median	17.0	-	17.0	-	17.0	-
	Maximum	30	-	25	-	30	-
	Unknown	9	-	4	-	13	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	9.5	-	9.6	-	9.5	-
	SD	2.08	-	2.03	-	2.06	-
	Minimum	2	-	2	-	2	-
	Median	10.0	-	10.0	-	10.0	-
	Maximum	13	-	13	-	13	-
Gender	**Female**	435	47.6	232	47.3	667	47.5
	Male	479	52.4	258	52.7	737	52.5
Race	**African heritage**	5	0.5	4	0.8	9	0.6
	White/Caucasian	878	96.1	474	96.7	1352	96.3
	Arabic/north African	9	1.0	3	0.6	12	0.9
	East/south east Asian	1	0.1	1	0.2	2	0.1
	South Asian	4	0.4	1	0.2	5	0.4
	American Hispanic	13	1.4	5	1.0	18	1.3
	Japanese	0	0.0	0	0.0	0	0.0
	Other	4	0.4	2	0.4	6	0.4
Height (cm)	**Mean**	58.9	-	58.9	-	58.9	-
	SD	3.45	-	3.39	-	3.43	-
	Median	59.0	-	59.0	-	59.0	-
	Unknown	1	-	2	-	3	-
Weight (kg)	**Mean**	5.6	-	5.6	-	5.6	-
	SD	0.90	-	0.87	-	0.89	-
	Median	5.5	-	5.6	-	5.5	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	**Mean**	16.0	-	16.0	-	16.0	-
	SD	1.58	-	1.64	-	1.60	-
	Median	15.9	-	16.0	-	15.9	-
	Unknown	1	-	2	-	3	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 13 Summary of demographic characteristics – Pooled countries – ATP cohort for immunogenicity

		HRV N = 794		Placebo N = 422		Total N = 1216	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at Dose 1 (weeks)	**Mean**	10.4	-	10.4	-	10.4	-
	SD	2.44	-	2.42	-	2.44	-
	Minimum	6	-	6	-	6	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	14	-	14	-	14	-
Age at Dose 2 (weeks)	**Mean**	17.2	-	17.3	-	17.2	-
	SD	2.88	-	2.99	-	2.92	-
	Minimum	10	-	10	-	10	-
	Median	17.0	-	17.0	-	17.0	-
	Maximum	25	-	25	-	25	-
Age at Visit 5 or at last contact if Visit 5 not performed (Months)	**Mean**	9.6	-	9.7	-	9.6	-
	SD	1.93	-	1.93	-	1.93	-
	Minimum	6	-	5	-	5	-
	Median	10.0	-	10.0	-	10.0	-
	Maximum	13	-	13	-	13	-
Gender	**Female**	374	47.1	205	48.6	579	47.6
	Male	420	52.9	217	51.4	637	52.4
Race	**African heritage**	4	0.5	4	0.9	8	0.7
	White/Caucasian	762	96.0	410	97.2	1172	96.4
	Arabic/north African	9	1.1	2	0.5	11	0.9
	East/south east Asian	1	0.1	0	0.0	1	0.1
	South Asian	3	0.4	1	0.2	4	0.3
	American Hispanic	11	1.4	4	0.9	15	1.2
	Japanese	0	0.0	0	0.0	0	0.0
	Other	4	0.5	1	0.2	5	0.4
Height (cm)	**Mean**	58.9	-	59.0	-	59.0	-
	SD	3.44	-	3.38	-	3.42	-
	Median	59.0	-	59.0	-	59.0	-
	Unknown	1	-	2	-	3	-
Weight (kg)	**Mean**	5.6	-	5.6	-	5.6	-
	SD	0.90	-	0.87	-	0.89	-
	Median	5.5	-	5.6	-	5.5	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	**Mean**	16.0	-	16.0	-	16.0	-
	SD	1.60	-	1.63	-	1.61	-
	Median	15.9	-	16.0	-	15.9	-
	Unknown	1	-	2	-	3	-

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 14 Summary of feeding criteria at Dose 1 and Dose 2 of HRV/Placebo, by country and for pooled countries – ATP cohort for immunogenicity

		HRV N = 794		Placebo N = 422		Total N = 1216	
Country	**Infant was breast fed at**	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	**Both doses**	148	81.3	69	76.7	217	79.8
	One dose	9	4.9	6	6.7	15	5.5
	None	25	13.7	15	16.7	40	14.7
Finland	**Both doses**	110	65.9	74	70.5	184	67.6
	One dose	19	11.4	16	15.2	35	12.9
	None	38	22.8	15	14.3	53	19.5
France	**Both doses**	25	30.1	15	34.9	40	31.7
	One dose	11	13.3	13	30.2	24	19.0
	None	47	56.6	15	34.9	62	49.2
Germany	**Both doses**	88	56.4	47	56.0	135	56.3
	One dose	26	16.7	10	11.9	36	15.0
	None	42	26.9	27	32.1	69	28.8
Italy	**Both doses**	7	53.8	5	55.6	12	54.5
	One dose	2	15.4	1	11.1	3	13.6
	None	4	30.8	3	33.3	7	31.8
Spain	**Both doses**	86	44.6	45	49.5	131	46.1
	One dose	46	23.8	20	22.0	66	23.2
	None	61	31.6	26	28.6	87	30.6
Pooled countries	**Both doses**	464	58.4	255	60.4	719	59.1
	One dose	113	14.2	66	15.6	179	14.7
	None	217	27.3	101	23.9	318	26.2

N = number of subjects in the considered group or in total (sum of both groups)
n/% = number/percentage of subjects in a given category, by country and for pooled countries

Supplement 15 Summary of co-administered vaccinations at Dose 1, by country – Total vaccinated cohort

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	**Any**	199	196	98.5	100	99	99.0	299	295	98.7
	DTPa-HBV-IPV/Hib		196	98.5		99	99.0		295	98.7
Finland	**Any**	1918	1917	99.9	972	972	100	2890	2889	100
	BCG		3	0.2		2	0.2		5	0.2
	DTPa-HBV-IPV/Hib		1917	99.9		972	100		2889	100
France	**Any**	95	95	100	51	51	100	146	146	100
	DTPa-HBV-IPV/Hib		95	100		51	100		146	100
	Prevenar		95	100		51	100		146	100
Germany	**Any**	190	188	98.9	99	99	100	289	287	99.3
	DTPa-HBV-IPV/Hib		188	98.9		99	100		287	99.3
	Prevenar		188	98.9		98	99.0		286	99.0
Italy	**Any**	15	15	100	10	10	100	25	25	100
	DTPa-HBV-IPV/Hib		15	100		10	100		25	100
Spain	**Any**	229	228	99.6	116	115	99.1	345	343	99.4
	DTPa-HBV-IPV/Hib		228	99.6		115	99.1		343	99.4
	Meningitec		228	99.6		115	99.1		343	99.4

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the first dose of HRV/Placebo

Supplement 16 Summary of co-administered vaccinations at Dose 2, by country – Total vaccinated cohort

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	**Any**	198	198	100	100	99	99.0	298	297	99.7
	DTPA-HBV-IPV/HIB		198	100		99	99.0		297	99.7
Finland	**Any**	1900	1900	100	965	964	99.9	2865	2864	100
	BCG		1	0.1		1	0.1		2	0.1
	DTPA-HBV-IPV/HIB		1900	100		964	99.9		2864	100
France	**Any**	95	95	100	51	51	100	146	146	100
	DTPA-IPV-HIB		95	100		51	100		146	100
	PREVENAR		95	100		51	100		146	100
Germany	**Any**	187	187	100	99	98	99.0	286	285	99.7
	DTPA-HBV-IPV/HIB		187	100		98	99.0		285	99.7
	PREVENAR		187	100		98	99.0		285	99.7
Italy	**Any**	15	15	100	10	10	100	25	25	100
	DTPA-HBV-IPV/HIB		15	100		10	100		25	100
Spain	**Any**	226	226	100	113	113	100	339	339	100
	DTPA-HBV-IPV/HIB		226	100		113	100		339	100
	MENINGITEC		226	100		113	100		339	100

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the second dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the second dose of HRV/Placebo

Supplement 17 Summary of vaccines other than HRV/Placebo administered before the day of Dose 1 of HRV/Placebo, by country – Total vaccinated cohort

		HRV				Placebo				Total			
Country	**Vaccine**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**
Czech Republic	**Any**	200	199	199	100	100	100	100	100	300	299	299	100
	BCG	199		199	100	100		100	100	299		299	100
	DTPA-HBV-IPV/HIB	1		1	0.5	0		0	0.0	1		1	0.3
Finland	**Any**	1912	1918	1912	99.7	967	972	967	99.5	2879	2890	2879	99.6
	BCG	1912		1912	99.7	967		967	99.5	2879		2879	99.6
France	**Any**	0	95	0	0.0	1	51	1	2.0	1	146	1	0.7
	BCG	0		0	0.0	1		1	2.0	1		1	0.7
Germany	**Any**	0	190	0	0	0	99	0	0	0	289	0	0
Italy	**Any**	0	15	0	0	0	10	0	0	0	25	0	0
Spain	**Any**	3	229	2	0.9	4	116	3	2.6	7	345	5	1.4
	DTPA-HBV-IPV/HIB	1		1	0.4	1		1	0.9	2		2	0.6
	HBV	1		1	0.4	2		2	1.7	3		3	0.9
	MENINGITEC	1		1	0.4	1		1	0.9	2		2	0.6

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of the HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine from birth up to the day preceding the administration of the first dose of the HRV/Placebo

= number of doses of the specified vaccine administered from birth up to the day preceding the administration of the first dose of the HRV/Placebo

Supplement 18 Summary of vaccines other than HRV/Placebo administered after the day of Dose 1 of HRV/Placebo and before the day of Dose 2 of HRV/Placebo, by country – Total vaccinated cohort

		HRV				Placebo				Total			
Country	**Vaccine**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**
Czech Republic	**Any**	0	199	0	0	0	100	0	0	0	299	0	0
Finland	**Any**	15	1918	11	0.6	6	972	5	0.5	21	2890	16	0.6
	DTPA-HBV-IPV/HIB	15		11	0.6	6		5	0.5	21		16	0.6
France	**Any**	0	95	0	0	0	51	0	0	0	146	0	0
Germany	**Any**	0	190	0	0.0	2	99	1	1.0	2	289	1	0.3
	DTPA-HBV-IPV/HIB	0		0	0.0	1		1	1.0	1		1	0.3
	PREVENAR	0		0	0.0	1		1	1.0	1		1	0.3
Italy	**Any**	0	15	0	0	0	10	0	0	0	25	0	0
Spain	**Any**	227	229	226	98.7	114	116	114	98.3	341	345	340	98.6
	PREVENAR	227		226	98.7	114		114	98.3	341		340	98.6

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of the HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine after the day of administration of the first dose of the HRV/Placebo up to the day preceding the second administration of the HRV/Placebo (*)

= number of doses of the specified vaccine administered after the day of administration of the first dose of the HRV/Placebo vaccine up to the day preceding the second administration of the HRV/Placebo vaccine (*)

(*) or up to the date of last contact at the conclusion of the first period (at Visit 5) if the second dose of the HRV/placebo vaccine was not administered

Supplement 19 Summary of vaccines other than HRV/Placebo administered after the day of Dose 2 of HRV/Placebo and up to 30 days post that day, by country – Total vaccinated cohort

		HRV				Placebo				Total			
Country	**Vaccine**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**
Czech Republic	**Any**	52	198	52	26.3	27	100	27	27.0	79	298	79	26.5
	DTPA-HBV-IPV/HIB	52		52	26.3	27		27	27.0	79		79	26.5
Finland	**Any**	0	1900	0	0.0	1	965	1	0.1	1	2865	1	0.0
	DTPA-IPV-HIB	0		0	0.0	1		1	0.1	1		1	0.0
France	**Any**	80	95	40	42.1	56	51	28	54.9	136	146	68	46.6
	DTPA-HBV-IPV/HIB	40		40	42.1	28		28	54.9	68		68	46.6
	PREVENAR	40		40	42.1	28		28	54.9	68		68	46.6
Germany	**Any**	121	187	61	32.6	64	99	32	32.3	185	286	93	32.5
	DTPA-HBV-IPV/HIB	61		61	32.6	32		32	32.3	93		93	32.5
	PREVENAR	60		60	32.1	32		32	32.3	92		92	32.2
Italy	**Any**	0	15	0	0	0	10	0	0	0	25	0	0
Spain	**Any**	161	226	161	71.2	80	113	80	70.8	241	339	241	71.1
	PREVENAR	161		161	71.2	80		80	70.8	241		241	71.1

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the second dose of the HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine after the day of administration of the second dose of the HRV/Placebo up to 30 days after that day (*)

= number of doses of the specified vaccine administered after the day of administration of the second dose of the HRV/Placebo up to 30 days after that day (*)

(*) or up to the date of last contact at the conclusion of the first period (at Visit 5), whichever came first

Supplement 20 Summary of co-administered vaccinations at Dose 1, by country – ATP cohort for efficacy

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	**Any**	193	190	98.4	97	96	99.0	290	286	98.6
	DTPA-HBV-IPV/HIB		190	98.4		96	99.0		286	98.6
Finland	**Any**	1893	1892	99.9	956	956	100	2849	2848	100
	DTPA-HBV-IPV/HIB		1892	99.9		956	100		2848	100
France	**Any**	95	95	100	50	50	100	145	145	100
	DTPA-HBV-IPV/HIB		95	100		50	100		145	100
	PREVENAR		95	100		50	100		145	100
Germany	**Any**	179	178	99.4	94	94	100	273	272	99.6
	DTPA-HBV-IPV/HIB		178	99.4		94	100		272	99.6
	PREVENAR		178	99.4		94	100		272	99.6
Italy	**Any**	15	15	100	10	10	100	25	25	100
	DTPA-HBV-IPV/HIB		15	100		10	100		25	100
Spain	**Any**	197	196	99.5	95	94	98.9	292	290	99.3
	DTPA-HBV-IPV/HIB		196	99.5		94	98.9		290	99.3
	MENINGITEC		196	99.5		94	98.9		290	99.3

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the first dose of HRV/Placebo

Supplement 21 Summary of co-administered vaccinations at Dose 2, by country – ATP cohort for efficacy

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	**Any**	193	193	100	97	96	99.0	290	289	99.7
	DTPA-HBV-IPV/HIB		193	100		96	99.0		289	99.7
Finland	**Any**	1893	1893	100	956	955	99.9	2849	2848	100
	DTPA-HBV-IPV/HIB		1893	100		955	99.9		2848	100
France	**Any**	95	95	100	50	50	100	145	145	100
	DTPA-IPV-HIB		95	100		50	100		145	100
	PREVENAR		95	100		50	100		145	100
Germany	**Any**	179	179	100	94	93	98.9	273	272	99.6
	DTPA-HBV-IPV/HIB		179	100		93	98.9		272	99.6
	PREVENAR		179	100		93	98.9		272	99.6
Italy	**Any**	15	15	100	10	10	100	25	25	100
	DTPA-HBV-IPV/HIB		15	100		10	100		25	100
Spain	**Any**	197	197	100	95	95	100	292	292	100
	DTPA-HBV-IPV/HIB		197	100		95	100		292	100
	MENINGITEC		197	100		95	100		292	100

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the second dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the second dose of HRV/Placebo

Supplement 22 Summary of co-administered vaccinations at Dose 1, by country – ATP cohort for immunogenicity

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	**Any**	182	179	98.4	90	89	98.9	272	268	98.5
	DTPA-HBV-IPV/HIB		179	98.4		89	98.9		268	98.5
Finland	**Any**	167	167	100	105	105	100	272	272	100
	DTPA-HBV-IPV/HIB		167	100		105	100		272	100
France	**Any**	83	83	100	43	43	100	126	126	100
	DTPA-HBV-IPV/HIB		83	100		43	100		126	100
	PREVENAR		83	100		43	100		126	100
Germany	**Any**	156	155	99.4	84	84	100	240	239	99.6
	DTPA-HBV-IPV/HIB		155	99.4		84	100		239	99.6
	PREVENAR		155	99.4		84	100		239	99.6
Italy	**Any**	13	13	100	9	9	100	22	22	100
	DTPA-HBV-IPV/HIB		13	100		9	100		22	100
Spain	**Any**	193	192	99.5	91	90	98.9	284	282	99.3
	DTPA-HBV-IPV/HIB		192	99.5		90	98.9		282	99.3
	MENINGITEC		192	99.5		90	98.9		282	99.3

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the first dose of HRV/Placebo

Supplement 23 Summary of co-administered vaccinations at Dose 2, by country – ATP cohort for immunogenicity

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Czech Republic	**Any**	182	182	100	90	89	98.9	272	271	99.6
	DTPA-HBV-IPV/HIB		182	100		89	98.9		271	99.6
Finland	**Any**	167	167	100	105	105	100	272	272	100
	DTPA-HBV-IPV/HIB		167	100		105	100		272	100
France	**Any**	83	83	100	43	43	100	126	126	100
	DTPA-IPV-HIB		83	100		43	100		126	100
	PREVENAR		83	100		43	100		126	100
Germany	**Any**	156	156	100	84	84	100	240	240	100
	DTPA-HBV-IPV/HIB		156	100		84	100		240	100
	PREVENAR		156	100		84	100		240	100
Italy	**Any**	13	13	100	9	9	100	22	22	100
	DTPA-HBV-IPV/HIB		13	100		9	100		22	100
Spain	**Any**	193	193	100	91	91	100	284	284	100
	DTPA-HBV-IPV/HIB		193	100		91	100		284	100
	MENINGITEC		193	100		91	100		284	100

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the second dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the second dose of HRV/Placebo

Supplement 24 Number of days between the second and third dose of childhood vaccination, by country – ATP cohort for immunogenicity

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Czech Republic	**N**	182	89	271
	Mean	35.8	34.8	35.5
	SD	8.68	7.63	8.35
	Minimum	27	21	21
	Q1	30.0	29.0	30.0
	Median	34.0	33.0	33.0
	Q3	36.0	36.0	36.0
	Maximum	85	67	85
France	**N**	83	43	126
	Mean	31.7	31.2	31.5
	SD	5.20	5.02	5.12
	Minimum	21	21	21
	Q1	28.0	28.0	28.0
	Median	31.0	30.0	31.0
	Q3	35.0	34.0	35.0
	Maximum	54	42	54
Germany	**N**	155	80	235
	Mean	39.0	37.0	38.3
	SD	15.17	11.98	14.17
	Minimum	21	21	21
	Q1	29.0	29.0	29.0
	Median	33.0	33.5	33.0
	Q3	49.0	44.5	48.0
	Maximum	111	84	111
Spain	**N**	193	91	284
	Mean	56.2	56.0	56.1
	SD	7.55	6.95	7.35
	Minimum	49	49	49
	Q1	49.0	49.0	49.0
	Median	54.0	54.0	54.0
	Q3	63.0	63.0	63.0
	Maximum	85	73	85

N = Number of subjects of the specified group or of the total (sum of both groups) who have been administered the second and the third dose of the childhood vaccine(s)
Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second and the third dose of the childhood vaccine(s)
Q1 = 25th percentile of the distribution of the number of days
Q3 = 75th percentile of the distribution of the number of days
SD = standard deviation of the distribution of the number of days
For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 of childhood vaccination in France) vaccine.

Supplement 25 Number of days between the third dose of childhood vaccination and the post-vaccination blood sample at Visit 3, by country – ATP cohort for immunogenicity

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Czech Republic	**N**	182	89	271
	Mean	26.2	26.6	26.3
	SD	10.83	10.80	10.80
	Minimum	-34	-27	-34
	Q1	22.0	21.0	22.0
	Median	28.0	29.0	28.0
	Q3	34.0	35.0	34.0
	Maximum	48	42	48
France	**N**	83	43	126
	Mean	33.0	32.7	32.9
	SD	5.58	4.62	5.25
	Minimum	20	21	20
	Q1	30.0	30.0	30.0
	Median	32.0	32.0	32.0
	Q3	35.0	35.0	35.0
	Maximum	55	47	55
Germany	**N**	155	80	235
	Mean	24.8	25.8	25.2
	SD	15.73	15.01	15.47
	Minimum	-50	-22	-50
	Q1	21.0	23.0	21.0
	Median	31.0	32.0	32.0
	Q3	34.0	34.5	34.0
	Maximum	50	50	50

N = Number of subjects in the considered group or in total (sum of both groups) who have been administered the third dose of the childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 3 available for at least one of the childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the third dose of the childhood vaccine(s) and the post-vaccination blood sampling at Visit 3

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Results for Finland and Italy are not presented as the third dose of the childhood vaccine(s) had not been administered yet in those countries at the time of Visit 5. Results for Spain are presented separately as the blood sampling following the third dose of childhood vaccination occurred at Visit 4.

For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 of childhood vaccination in France) vaccine.

Supplement 26 Number of days between the third dose of childhood vaccination and the post-vaccination blood sample at Visit 4, in Spain – ATP cohort for immunogenicity

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Spain	**N**	188	91	279
	Mean	35.3	34.9	35.2
	SD	4.08	4.34	4.16
	Minimum	26	21	21
	Q1	32.5	31.0	32.0
	Median	35.0	35.0	35.0
	Q3	38.0	36.0	37.0
	Maximum	45	48	48

N = Number of subjects in the considered group or in total (sum of both groups) who have been administered the third dose of the childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 4 available for at least one of the childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the third dose of the childhood vaccine(s) and the post-vaccination blood sampling at Visit 4

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Spain was the only country with the blood sampling following the third dose of childhood vaccination occurring at Visit 4.

For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa vaccine.

Supplement 27 Number of days between the second dose of childhood vaccination and the post-vaccination blood sample at Visit 3, by country – ATP cohort for immunogenicity

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Finland	**N**	167	105	272
	Mean	36.5	36.7	36.6
	SD	4.17	4.77	4.40
	Minimum	30	27	27
	Q1	33.0	33.0	33.0
	Median	35.0	36.0	36.0
	Q3	41.0	41.0	41.0
	Maximum	48	48	48
Italy	**N**	13	9	22
	Mean	35.8	36.4	36.1
	SD	4.39	4.80	4.46
	Minimum	30	30	30
	Q1	35.0	34.0	34.0
	Median	36.0	37.0	36.5
	Q3	37.0	37.0	37.0
	Maximum	45	45	45
Spain	**N**	191	90	281
	Mean	55.8	55.6	55.8
	SD	7.02	6.84	6.95
	Minimum	49	49	49
	Q1	49.0	49.0	49.0
	Median	54.0	54.0	54.0
	Q3	63.0	61.0	63.0
	Maximum	79	73	79

N = Number of subjects in the considered group or in total (sum of both groups) who have been administered the second dose of the childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 3 available for at least one of the childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second dose of the childhood vaccine(s) and the post-vaccination blood sampling at Visit 3

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Results are presented for Finland, Italy and Spain as only these countries had the blood sampling at Visit 3 following the second dose of childhood vaccination.

For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 of childhood vaccination in France) vaccine.

Supplement 28 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Czech Republic – ATP cohort for immunogenicity

	HRV N = 182		Placebo N = 90		Total N = 272	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	0	0.0	1	1.1	1	0.4
2	34	18.7	16	17.8	50	18.4
3	148	81.3	73	81.1	221	81.3
At least one	182	100	90	100	272	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 29 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Finland – ATP cohort for immunogenicity

	HRV N = 167		Placebo N = 105		Total N = 272	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	167	100	105	100	272	100
At least one	167	100	105	100	272	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 30 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - France – ATP cohort for immunogenicity

	HRV N = 83		Placebo N = 43		Total N = 126	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	2	2.4	0	0.0	2	1.6
2	81	97.6	43	100	124	98.4
At least one	83	100	43	100	126	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 31 Distribution of the total number of doses by subject of Infanrix Polio Hib received from Visit 1 up to 21 days before blood sample at Visit 3 - France – ATP cohort for immunogenicity

	HRV N = 83		Placebo N = 43		Total N = 126	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	83	100	43	100	126	100
At least one	83	100	43	100	126	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Infanrix Polio Hib antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 32 Distribution of the total number of doses by subject of Prevenar received from Visit 1 up to 21 days before blood sample at Visit 3 - France – ATP cohort for immunogenicity

	HRV N = 83		Placebo N = 43		Total N = 126	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	1	1.2	0	0.0	1	0.8
3	82	98.8	43	100	125	99.2
At least one	83	100	43	100	126	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Prevenar antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 33 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Germany – ATP cohort for immunogenicity

	HRV N = 155		Placebo N = 84		Total N = 239	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	37	23.9	23	27.4	60	25.1
3	118	76.1	61	72.6	179	74.9
At least one	155	100	84	100	239	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 34 Distribution of the total number of doses by subject of Prevenar received from Visit 1 up to 21 days before blood sample at Visit 3 - Germany – ATP cohort for immunogenicity

	HRV N = 155		Placebo N = 84		Total N = 239	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	39	25.2	23	27.4	62	25.9
3	116	74.8	61	72.6	177	74.1
At least one	155	100	84	100	239	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Prevenar antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 35 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Italy – ATP cohort for immunogenicity

	HRV N = 13		Placebo N = 9		Total N = 22	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	13	100	9	100	22	100
At least one	13	100	9	100	22	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 36 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Spain – ATP cohort for immunogenicity

	HRV N = 191		Placebo N = 90		Total N = 281	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	191	100	90	100	281	100
At least one	191	100	90	100	281	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample 2 - taken at Visit 3 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 37 Distribution of the total number of doses by subject of Meningitec received from Visit 1 up to 21 days before blood sample at Visit 3 - Spain – ATP cohort for immunogenicity

	HRV N = 191		Placebo N = 90		Total N = 281	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	191	100	90	100	281	100
At least one	191	100	90	100	281	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 available for at least one of the Meningitec antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 38 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 4 - Spain – ATP cohort for immunogenicity

	HRV N = 188		Placebo N = 91		Total N = 279	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
3	188	100	91	100	279	100
At least one	188	100	91	100	279	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 4 available for at least one of the Infanrix Hexa antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 4

Supplement 39 Distribution of the total number of doses by subject of Meningitec received from Visit 1 up to 21 days before blood sample at Visit 4 - Spain – ATP cohort for immunogenicity

	HRV N = 188		Placebo N = 91		Total N = 279	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
3	188	100	91	100	279	100
At least one	188	100	91	100	279	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 4 available for at least one of the Meningitec antigens

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 4

Supplement 40 Summary of co-administered vaccinations at Dose 1 – Finland – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Finland	**Any**	186	186	100	114	114	100	300	300	100
	DTPA-HBV-IPV/HIB		186	100		114	100		300	100

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the first dose of HRV/Placebo

Supplement 41 Summary of co-administered vaccinations at Dose 2 – Finland – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV			Placebo			Total		
Country	**Vaccine**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Finland	**Any**	184	184	100	113	113	100	297	297	100
	DTPA-HBV-IPV/HIB		184	100		113	100		297	100

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the second dose of HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine on the same day as the second dose of HRV/Placebo

Supplement 42 Summary of vaccinations other than HRV/Placebo administered before the day of Dose 1 of HRV/Placebo – Finland – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV				Placebo				Total			
Country	**Vaccine**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**
Finland	**Any**	186	186	186	100	113	114	113	99.1	299	300	299	99.7
	BCG	186		186	100	113		113	99.1	299		299	99.7

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of the HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine from birth up to the day preceding the administration of the first dose of the HRV/Placebo

= number of doses of the specified vaccine administered from birth up to the day preceding the administration of the first dose of the HRV/Placebo

Supplement 43 Summary of vaccinations other than HRV/Placebo administered after the day of Dose 1 of HRV/Placebo and before the day of Dose 2 of HRV/Placebo – Finland – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV				Placebo				Total			
Country	**Vaccine**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**
Finland	**Any**	1	186	1	0.5	1	114	1	0.9	2	300	2	0.7
	DTPA-HBV-IPV/HIB	1		1	0.5	1		1	0.9	2		2	0.7

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the first dose of the HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine after the day of administration of the first dose of the HRV/Placebo up to the day preceding the second administration of the HRV/Placebo (*)

= number of doses of the specified vaccine administered after the day of administration of the first dose of the HRV/Placebo up to the day preceding the second administration of the HRV/Placebo (*)

(*) or up to the date of last contact at the conclusion of the first period (at Visit 5) if the second dose of the HRV/placebo vaccine was not administered

Supplement 44 Summary of vaccinations other than HRV/Placebo administered after the day of Dose 2 of HRV/Placebo and up to 30 days post that day – Finland – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV				Placebo				Total			
Country	**Vaccine**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**	**#**	**N**	**n**	**%**
Finland	**Any**	0	184	0	0	0	113	0	0	0	297	0	0

N = number of subjects in the considered group or in total (sum of both groups), for the specified country, having received the second dose of the HRV/Placebo

n/% = number/percentage of subjects having received at least one dose of the specified vaccine after the day of administration of the second dose of the HRV/Placebo up to 30 days after that day (*)

= number of doses of the specified vaccine administered after the day of administration of the second dose of the HRV/Placebo up to 30 days after that day (*)

(*) or up to the date of last contact at the conclusion of the first period (at Visit 5), whichever came first

Supplement 45 Number of days between the second and third dose of childhood vaccination, by country – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Czech Republic	**N**	198	99	297
	Mean	36.2	35.7	36.0
	SD	9.19	8.52	8.96
	Minimum	27	21	21
	Q1	30.0	30.0	30.0
	Median	34.0	34.0	34.0
	Q3	37.0	37.0	37.0
	Maximum	85	74	85
France	**N**	93	50	143
	Mean	32.6	32.0	32.4
	SD	7.73	6.37	7.26
	Minimum	21	21	21
	Q1	28.0	28.0	28.0
	Median	31.0	30.0	31.0
	Q3	35.0	35.0	35.0
	Maximum	83	52	83
Germany	**N**	180	94	274
	Mean	39.1	37.9	38.7
	SD	14.92	13.23	14.35
	Minimum	21	21	21
	Q1	29.0	29.0	29.0
	Median	33.0	34.0	33.0
	Q3	48.5	46.0	48.0
	Maximum	111	91	111
Spain	**N**	225	113	338
	Mean	56.3	56.4	56.4
	SD	7.66	7.78	7.69
	Minimum	41	41	41
	Q1	49.0	49.0	49.0
	Median	54.0	55.0	54.0
	Q3	63.0	63.0	63.0
	Maximum	85	89	89

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the second and the third dose of the childhood vaccine(s)
Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second and the third dose of the childhood vaccine(s)
Q1 = 25th percentile of the distribution of the number of days
Q3 = 75th percentile of the distribution of the number of days
SD = standard deviation of the distribution of the number of days
- Results for Finland and Italy are not presented as the third dose of the childhood vaccine(s) had not been administered yet in those countries at the time of Visit 5
- For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 in France) vaccine.

Supplement 46 Number of days between the third dose of childhood vaccination and the post-vaccination blood sample at Visit 3, by country – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Czech Republic	**N**	195	99	294
	Mean	26.1	27.1	26.4
	SD	11.43	10.72	11.19
	Minimum	-34	-27	-34
	Q1	22.0	21.0	21.0
	Median	28.0	29.0	28.0
	Q3	34.0	35.0	34.0
	Maximum	48	44	48
France	**N**	93	49	142
	Mean	33.9	33.5	33.8
	SD	6.66	5.79	6.35
	Minimum	20	21	20
	Q1	31.0	30.0	30.0
	Median	33.0	33.0	33.0
	Q3	36.0	35.0	36.0
	Maximum	65	59	65
Germany	**N**	177	93	270
	Mean	26.2	26.9	26.4
	SD	16.36	15.48	16.04
	Minimum	-50	-22	-50
	Q1	24.0	25.0	24.0
	Median	32.0	32.0	32.0
	Q3	35.0	35.0	35.0
	Maximum	74	57	74

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the third dose of the childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 3 available for at least one of the childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the third dose of the childhood vaccine(s) and the post-vaccination blood sampling at Visit 3

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

- For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 in France) vaccine.

Supplement 47 Number of days between the third dose of childhood vaccination and the post-vaccination blood sample at Visit 4, in Spain – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Spain	**N**	220	113	333
	Mean	35.7	34.9	35.5
	SD	4.85	4.26	4.67
	Minimum	26	21	21
	Q1	33.0	32.0	32.0
	Median	35.0	35.0	35.0
	Q3	39.0	36.0	38.0
	Maximum	69	48	69

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the third dose of the childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 4 available for at least one of the childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the third dose of the childhood vaccine(s) and the post-vaccination blood sampling at Visit 4

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

- For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 in France) vaccine.

Supplement 48 Number of days between the second dose of childhood vaccination and the post-vaccination blood sample at Visit 3, by country – Total vaccinated cohort for the immunogenicity and reactogenicity subset

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Finland	**N**	179	110	289
	Mean	36.7	36.8	36.8
	SD	4.75	4.99	4.83
	Minimum	30	27	27
	Q1	33.0	33.0	33.0
	Median	35.0	36.0	36.0
	Q3	41.0	41.0	41.0
	Maximum	57	49	57
Italy	**N**	15	10	25
	Mean	35.9	40.5	37.7
	SD	4.09	13.60	9.19
	Minimum	30	30	30
	Q1	35.0	34.0	35.0
	Median	36.0	37.0	37.0
	Q3	37.0	42.0	37.0
	Maximum	45	77	77
Spain	**N**	222	112	334
	Mean	55.9	55.8	55.9
	SD	7.24	7.49	7.31
	Minimum	41	41	41
	Q1	49.0	49.0	49.0
	Median	54.0	54.0	54.0
	Q3	63.0	61.5	62.0
	Maximum	82	89	89

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the second dose of the childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 3 available for at least one of the childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second dose of the childhood vaccine(s) and the post-vaccination blood sampling at Visit 3

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

- For countries where the childhood vaccination involved several co-administered vaccines and those vaccines could not be administered on the same day, the date of administration of the childhood vaccines was set as the date of administration of the Infanrix Hexa (or Infanrix Polio Hib for Dose 2 in France) vaccine.

Supplement 49 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Czech Republic – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 195		Placebo N = 100		Total N = 295	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	0	0.0	1	1.0	1	0.3
2	39	20.0	18	18.0	57	19.3
3	156	80.0	81	81.0	237	80.3
At least one	195	100	100	100	295	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Hexa antigens available
n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 50 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Finland – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 179		Placebo N = 110		Total N = 289	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	179	100	110	100	289	100
At least one	179	100	110	100	289	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Hexa antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 51 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - France – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 93		Placebo N = 49		Total N = 142	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	2	2.2	0	0.0	2	1.4
2	91	97.8	49	100	140	98.6
At least one	93	100	49	100	142	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Hexa antigens available
n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 52 Distribution of the total number of doses by subject of Infanrix Polio Hib received from Visit 1 up to 21 days before blood sample at Visit 3 - France – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 93		Placebo N = 49		Total N = 142	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	93	100	49	100	142	100
At least one	93	100	49	100	142	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Polio Hib antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 53 Distribution of the total number of doses by subject of Prevenar received from Visit 1 up to 21 days before blood sample at Visit 3 - France – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 93		Placebo N = 49		Total N = 142	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	1	1.1	0	0.0	1	0.7
3	92	98.9	49	100	141	99.3
At least one	93	100	49	100	142	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Prevenar antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 54 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Germany – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 177		Placebo N = 98		Total N = 275	
Number of doses received	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
2	41	23.2	26	26.5	67	24.4
3	136	76.8	72	73.5	208	75.6
At least one	177	100	98	100	275	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Hexa antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 55 Distribution of the total number of doses by subject of Prevenar received from Visit 1 up to 21 days before blood sample at Visit 3 - Germany – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 178		Placebo N = 98		Total N = 276	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	44	24.7	26	26.5	70	25.4
3	134	75.3	72	73.5	206	74.6
At least one	178	100	98	100	276	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Prevenar antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 56 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Italy – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 15		Placebo N = 10		Total N = 25	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	15	100	10	100	25	100
At least one	15	100	10	100	25	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Hexa antigens available

n/% = number of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 57 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 3 - Spain – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 222		Placebo N = 112		Total N = 334	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	222	100	112	100	334	100
At least one	222	100	112	100	334	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Infanrix Hexa antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 58 Distribution of the total number of doses by subject of Meningitec received from Visit 1 up to 21 days before blood sample at Visit 3 - Spain – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 222		Placebo N = 112		Total N = 334	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
2	222	100	112	100	334	100
At least one	222	100	112	100	334	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 3 for at least one of the Meningitec antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 3

Supplement 59 Distribution of the total number of doses by subject of Infanrix Hexa received from Visit 1 up to 21 days before blood sample at Visit 4 - Spain – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 220		Placebo N = 113		Total N = 333	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
3	220	100	113	100	333	100
At least one	220	100	113	100	333	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 4 for at least one of the Infanrix Hexa antigens available

n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 4

Supplement 60 Distribution of the total number of doses by subject of Meningitec received from Visit 1 up to 21 days before blood sample at Visit 4 - Spain – Total vaccinated cohort for the immunogenicity and reactogenicity subset

	HRV N = 220		Placebo N = 113		Total N = 333	
Number of doses	**n**	**%**	**n**	**%**	**n**	**%**
3	220	100	113	100	333	100
At least one	220	100	113	100	333	100

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at Visit 4 for at least one of the Meningitec antigens available

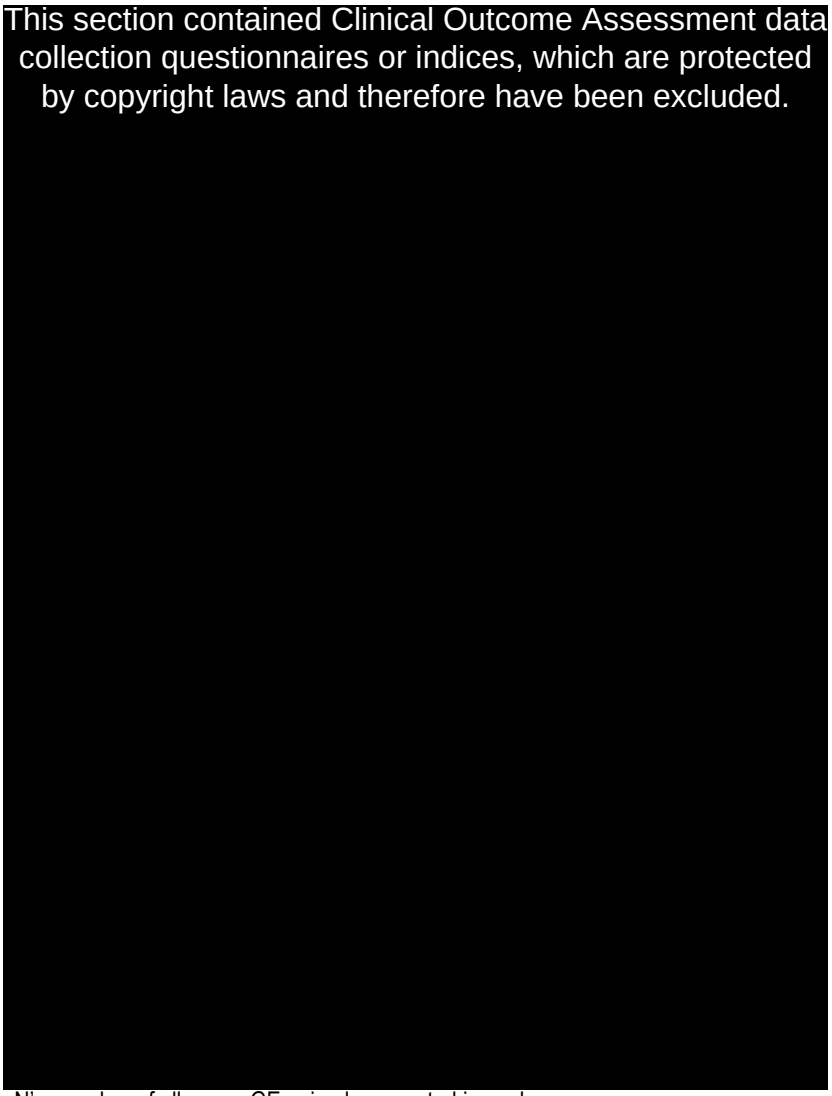
n/% = number/percentage of subjects having received the specified number of doses of the vaccine from the day of Visit 1 up to 21 days before the day of blood sampling at Visit 4

Supplement 61 Duration (in years) of the follow-up period from 2 weeks after Dose 2 up Visit 5 - ATP cohort for efficacy

Duration (years) of follow-up period	HRV N= 2572	Placebo N= 1302
Total	1216.9	620.8
Mean	0.473	0.477
SD	0.100	0.099
Minimum	0.027	0.132
Q1	0.400	0.405
Median	0.496	0.501
Q3	0.548	0.551
Maximum	0.696	0.696

N = number of subjects included in each group
Total = sum of follow-up period expressed in year
SD = standard deviation
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 62 Characteristics (based on Vesikari scale) of all cause GE episodes reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy



N' = number of all cause 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 63 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 5 – ATP cohort for efficacy

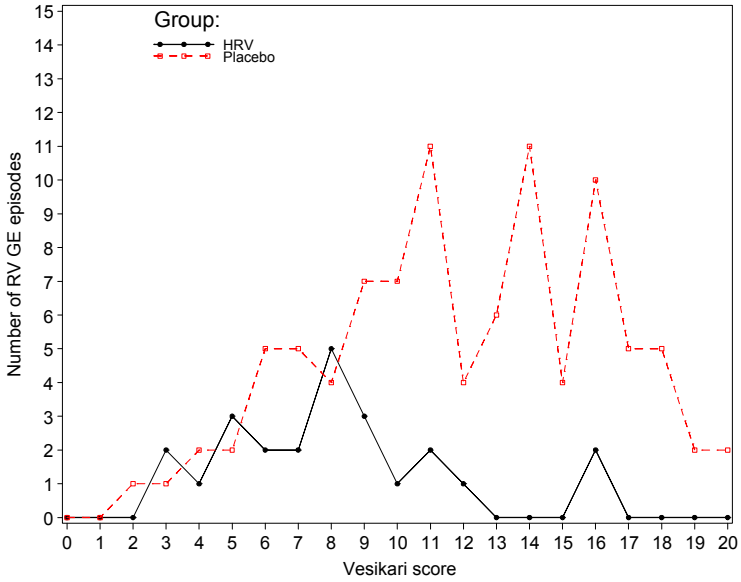
Category	HRV N'= 647 n	%	Placebo N'= 413 n	%
No stools collected	42	6.5	34	8.2
Stools collected but no results available*	12	1.9	10	2.4
No stool results available	54	8.3	44	10.7

N' = number of GE episodes reported

n/% = number/percentage of GE episodes within the specified category

* = due to quantity not sufficient or stool sample not tested

Supplement 64 Distribution of Vesikari score for RV GE reported from 2 weeks after Dose 2 up to Visit 5 – ATP cohort for efficacy



Supplement 65 Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV N= 2572		Placebo N= 1302	
	n	%	n	%
Any	24	0.9	94	7.2
G1 wild type	4	0.2	46	3.5
G2	3	0.1	4	0.3
G3	1	0.0	5	0.4
G4	3	0.1	13	1.0
G9	13	0.5	27	2.1
P4	3	0.1	3	0.2
P8 wild type	21	0.8	90	6.9
Unknown P type*	0	0.0	1	0.1

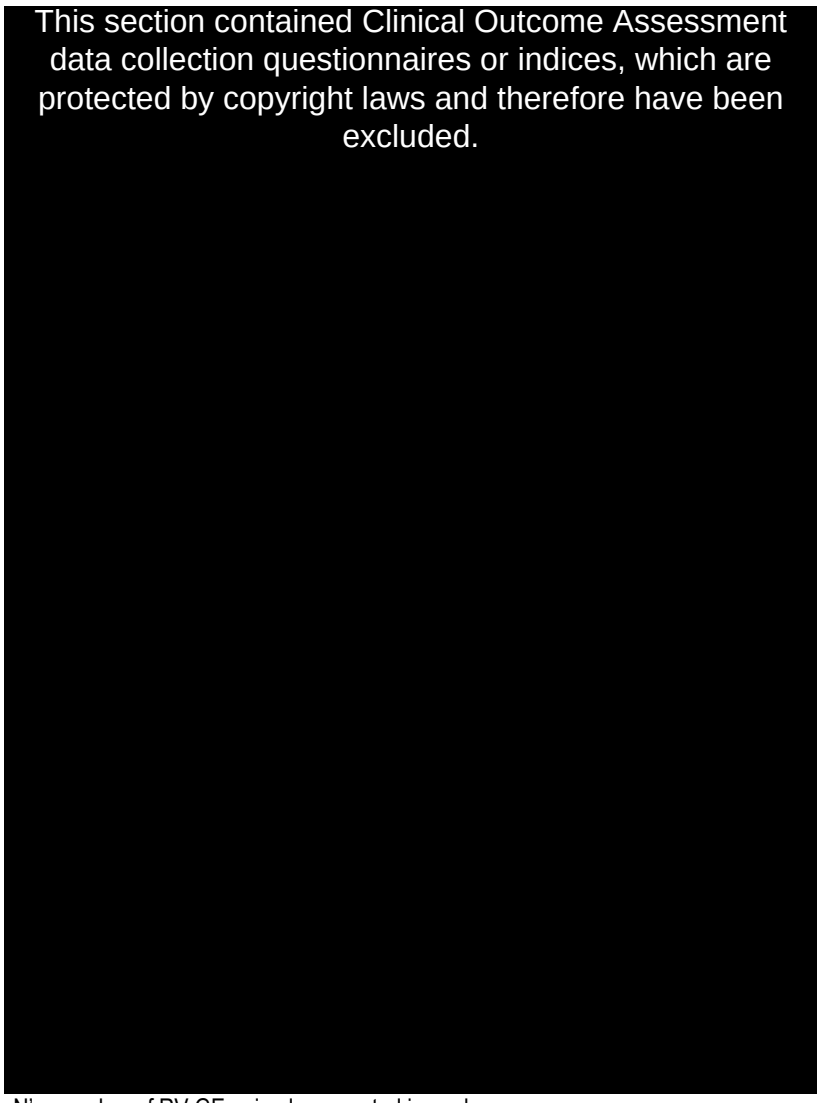
N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype in each group
Any = number of subjects reporting at least one RV GE episode, whatever the serotype
* = not typable

Supplement 66 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5, by G serotype and P genotype - ATP cohort for efficacy

Country	Serotype	HRV N'= 24 n	%	Placebo N'= 94 N	%
Czech Republic	**G9 and P8wt**	0	0.0	1	25.0
	G2 and P4	1	50.0	0	0.0
	G1wt and P8wt	0	0.0	3	75.0
	G4 and P8wt	1	50.0	0	0.0
Finland	**G2 and unknown P type**	0	0.0	1	1.2
	G9 and P8wt	12	63.2	22	26.2
	G2 and P4	2	10.5	3	3.6
	G1w and G4 and P8wt	0	0.0	1	1.2
	G1wt and P8wt	3	15.8	41	48.8
	G3 and P8wt	1	5.3	5	6.0
	G4 and P8wt	1	5.3	11	13.1
France	**G9 and P8wt**	1	50.0	4	80.0
	G1wt and P8wt	1	50.0	1	20.0
Germany	**G4 and P8wt**	1	100	0	0.0
Spain	**G4 and P8wt**	0	0.0	1	100
All countries	**G2 and unknown P type**	0	0.0	1	1.1
	G9 and P8wt	13	54.2	27	28.7
	G2 and P4	3	12.5	3	3.2
	G1w and G4 and P8wt	0	0.0	1	1.1
	G1wt and P8wt	4	16.7	45	47.9
	G3 and P8wt	1	4.2	5	5.3
	G4 and P8wt	3	12.5	12	12.8

N' = number of RV GE episodes reported
n/% = number/percentage of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type

Supplement 67 Characteristics (based on Vesikari scale) of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy



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 68 Characteristics (based on Vesikari scale) of RV GE episodes of G1 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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 69 Characteristics (based on Vesikari scale) of RV GE episodes of G9 with no other G type reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

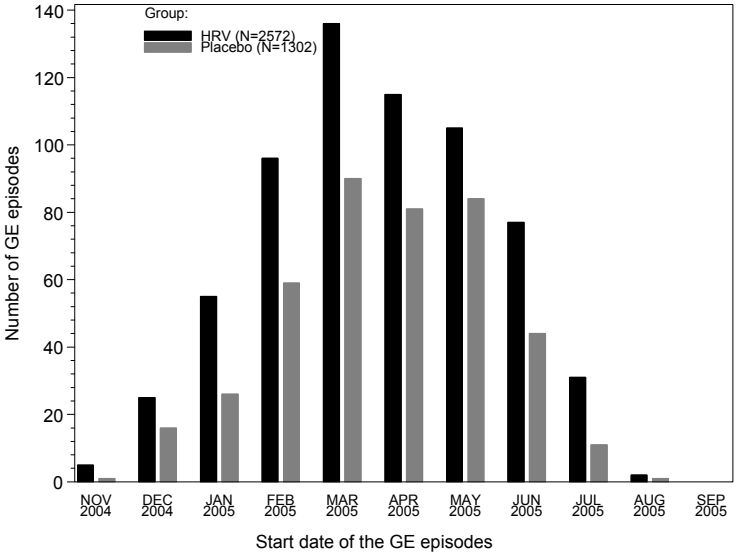
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 70 Characteristics (based on Vesikari scale) of RV GE episodes of G4 with no other G type reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

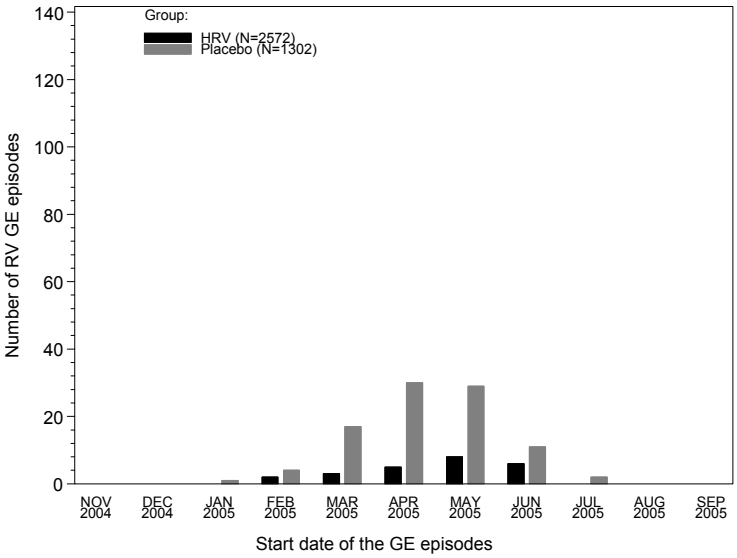
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 71 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – All countries – ATP efficacy cohort



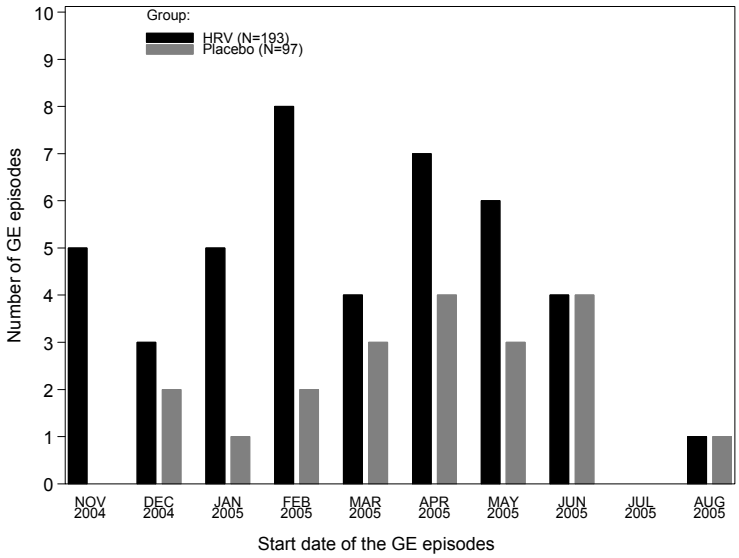
N = number of subjects included in each group

Supplement 72 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – All countries – ATP efficacy cohort



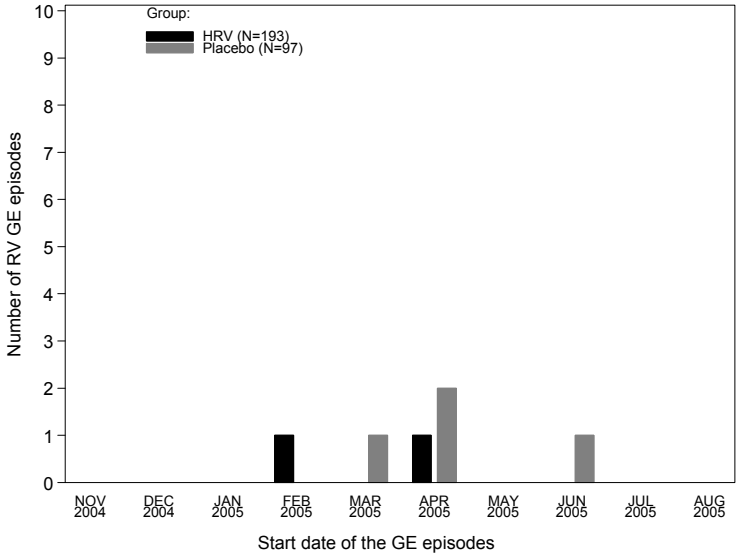
N = number of subjects included in each group

Supplement 73 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Czech Republic – ATP efficacy cohort



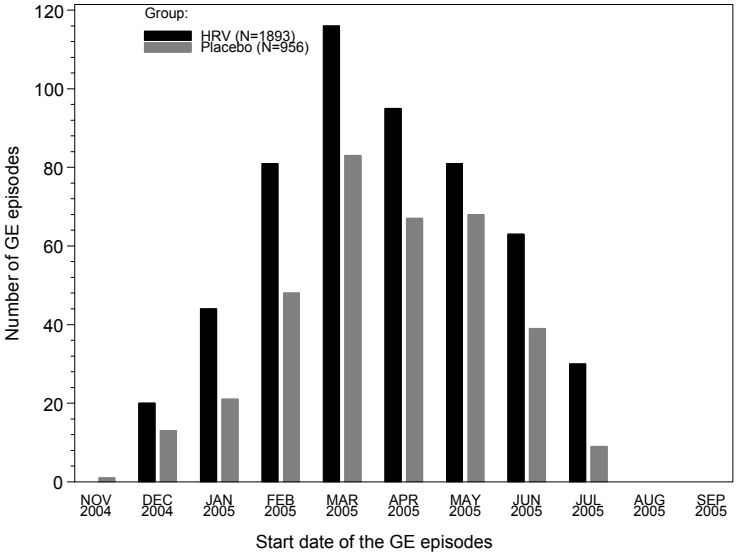
N = number of subjects included in each group

Supplement 74 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Czech Republic – ATP efficacy cohort



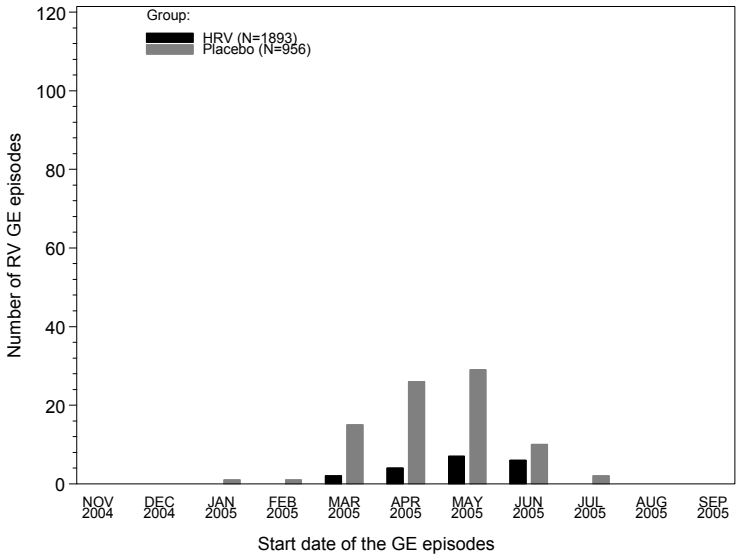
N = number of subjects included in each group

Supplement 75 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Finland – ATP efficacy cohort



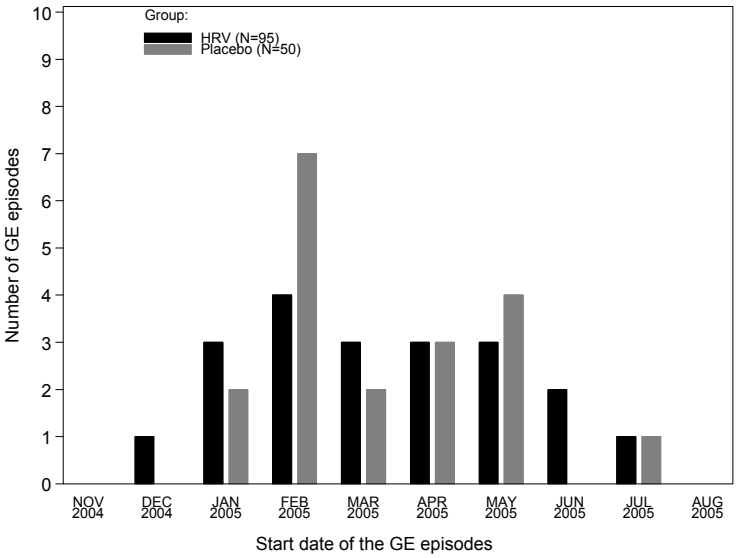
N = number of subjects included in each group

Supplement 76 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Finland – ATP efficacy cohort



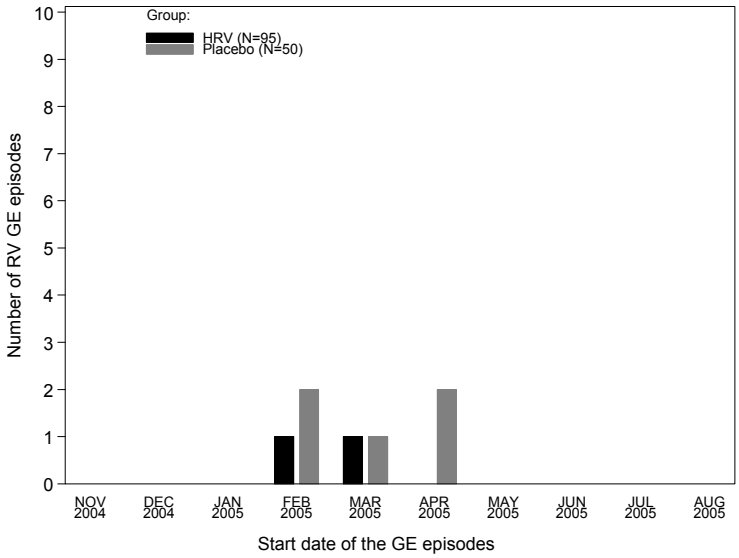
N = number of subjects included in each group

Supplement 77 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – France – ATP efficacy cohort



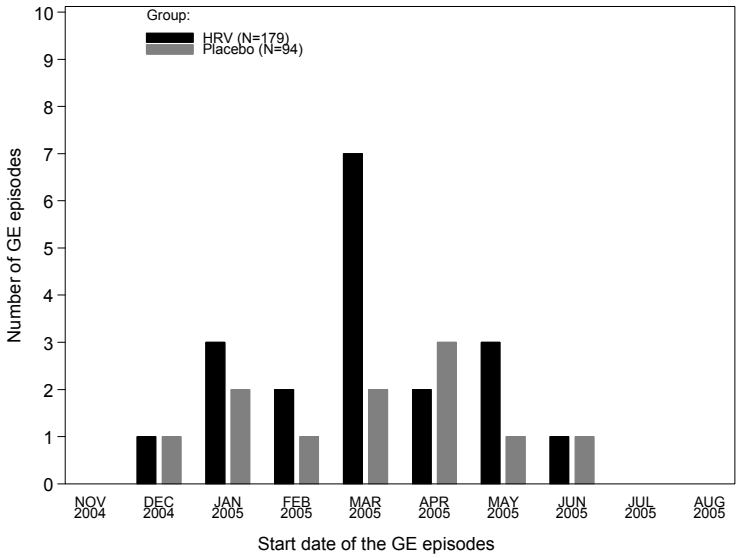
N = number of subjects included in each group

Supplement 78 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – France – ATP efficacy cohort



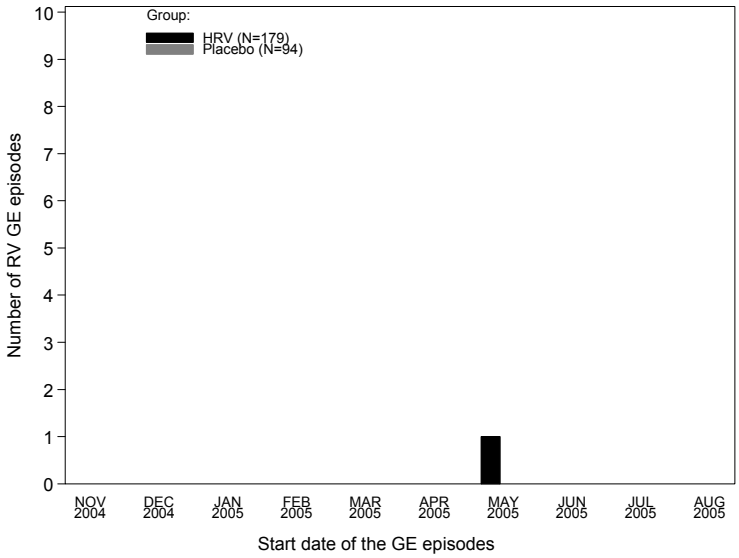
N = number of subjects included in each group

Supplement 79 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Germany – ATP efficacy cohort



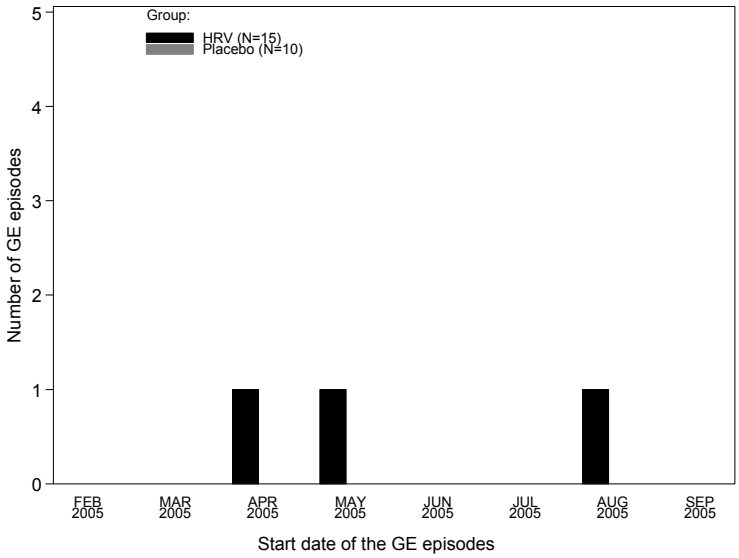
N = number of subjects included in each group

Supplement 80 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Germany – ATP efficacy cohort



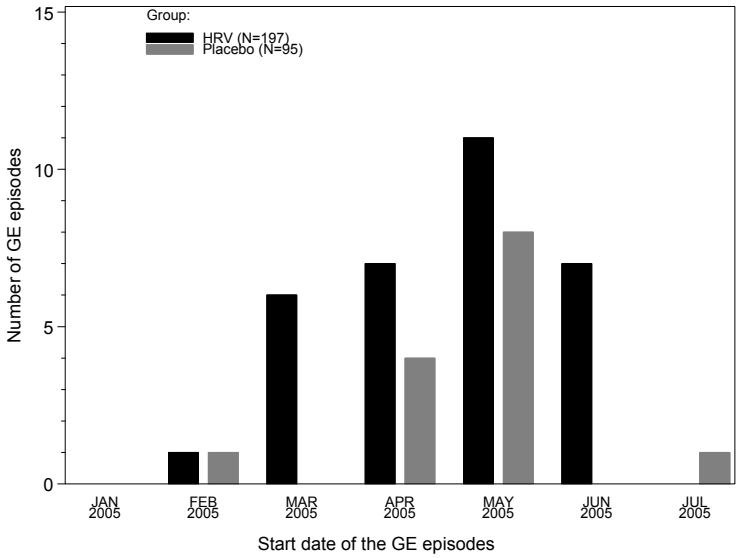
N = number of subjects included in each group

Supplement 81 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Italy – ATP efficacy cohort



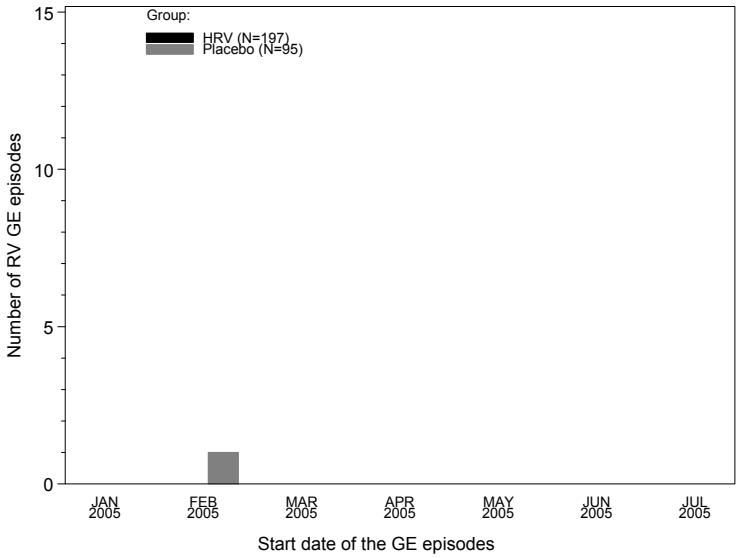
N = number of subjects included in each group

Supplement 82 Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Spain – ATP efficacy cohort



N = number of subjects included in each group

Supplement 83 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 – Spain – ATP efficacy cohort



N = number of subjects included in each group

Supplement 84 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5 - ATP efficacy cohort

Severity using Vesikari scale	Group	N	n/N n	%	95%CI LL	UL	Vaccine Efficacy %	95%CI LL	UL	P-value
≥11	**HRV**	2572	5	0.2	0.1	0.5	95.8	89.6	98.7	<0.001
	Placebo	1302	60	4.6	3.5	5.9				
≥12	**HRV**	2572	3	0.1	0.0	0.3	96.9	90.4	99.4	<0.001
	Placebo	1302	49	3.8	2.8	4.9				
≥13	**HRV**	2572	2	0.1	0.0	0.3	97.8	91.4	99.7	<0.001
	Placebo	1302	45	3.5	2.5	4.6				
≥14	**HRV**	2572	2	0.1	0.0	0.3	97.4	90.0	99.7	<0.001
	Placebo	1302	39	3.0	2.1	4.1				
≥15	**HRV**	2572	2	0.1	0.0	0.3	96.4	85.7	99.6	<0.001
	Placebo	1302	28	2.2	1.4	3.1				
≥16	**HRV**	2572	2	0.1	0.0	0.3	95.8	83.0	99.5	<0.001
	Placebo	1302	24	1.8	1.2	2.7				
≥17	**HRV**	2572	0	0.0	0.0	0.1	100	84.7	100	<0.001
	Placebo	1302	14	1.1	0.6	1.8				
≥18	**HRV**	2572	0	0.0	0.0	0.1	100	74.4	100	<0.001
	Placebo	1302	9	0.7	0.3	1.3				
≥19	**HRV**	2572	0	0.0	0.0	0.1	100	23.3	100	0.013
	Placebo	1302	4	0.3	0.1	0.8				
≥20	**HRV**	2572	0	0.0	0.0	0.1	100	-169.5	100	0.113
	Placebo	1302	2	0.2	0.0	0.6				

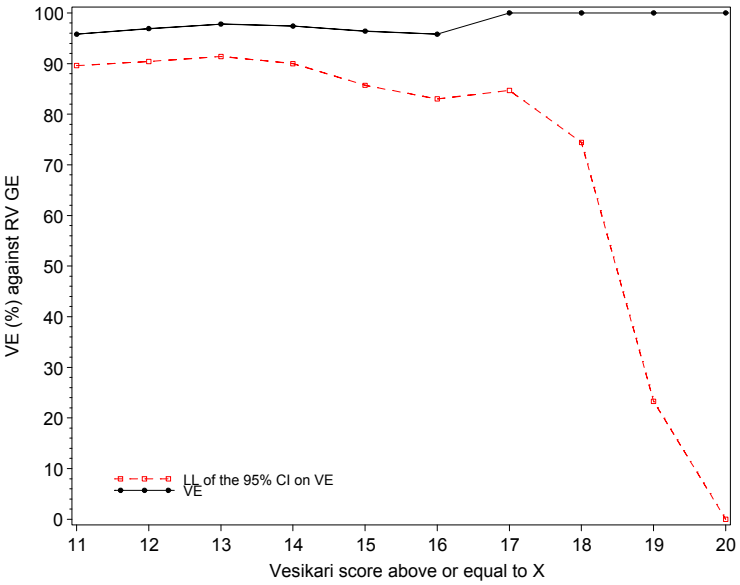
N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Vesikari scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 85 Efficacy of the vaccine against RV GE episodes with a score greater than or equal to X on the Vesikari scale from 2 weeks after Dose 2 up to Visit 5 – ATP efficacy cohort



Y-axis has been cut at 0

Supplement 86 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by status of anti-rotavirus IgA antibodies concentrations at Visit 3 - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 3	Group	N	n/N n	%	95%CI LL	UL	Vaccine Efficacy %	95%CI LL	UL	P-value
Positive	**HRV**	711	2	0.3	0.0	1.0	95.6	39.8	99.7	0.010
	Placebo	31	2	6.5	0.8	21.4				
Negative	**HRV**	110	2	1.8	0.2	6.4	58.1	-75.1	95.3	0.275
	Placebo	415	18	4.3	2.6	6.8				
Unknown	**HRV**	1751	20	1.1	0.7	1.8	86.8	78.1	92.4	<0.001
	Placebo	856	74	8.6	6.8	10.7				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group, by status of anti-rotavirus IgA antibodies concentrations at Visit 3

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 87 Percentage of subjects reporting severe (Vesikari scale) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by status of anti-rotavirus IgA antibodies concentrations at Visit 3 - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 3	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Positive	**HRV**	711	1	0.1	0.0	0.8	-infinity	-infinity	99.9	1.000
	Placebo	31	0	0.0	0.0	11.2				
Negative	**HRV**	110	0	0.0	0.0	3.3	100	-91.1	100	0.215
	Placebo	415	9	2.2	1.0	4.1				
Unknown	**HRV**	1751	4	0.2	0.1	0.6	96.2	89.6	99.0	<0.001
	Placebo	856	51	6.0	4.5	7.8				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group, by status of anti-rotavirus IgA antibodies concentrations at Visit 3

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 88 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by feeding criteria - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Breast feeding	Group	N	n	%	LL	UL	%	LL	UL	P-value
For at least one dose	HRV	2005	20	1.0	0.6	1.5	86.0	76.8	91.9	<0.001
	Placebo	1041	74	7.1	5.6	8.8				
At none of the doses	HRV	567	4	0.7	0.2	1.8	90.8	72.5	97.7	<0.001
	Placebo	261	20	7.7	4.7	11.6				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group, by feeding criteria

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 89 Percentage of subjects reporting severe (Vesikari) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by feeding criteria - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Breast feeding	Group	N	n	%	LL	UL	%	LL	UL	P-value
For at least one dose	HRV	2005	4	0.2	0.1	0.5	95.7	88.2	98.9	<0.001
	Placebo	1041	48	4.6	3.4	6.1				
At none of the doses	HRV	567	1	0.2	0.0	1.0	96.2	74.1	99.9	<0.001
	Placebo	261	12	4.6	2.4	7.9				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group, by feeding criteria

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

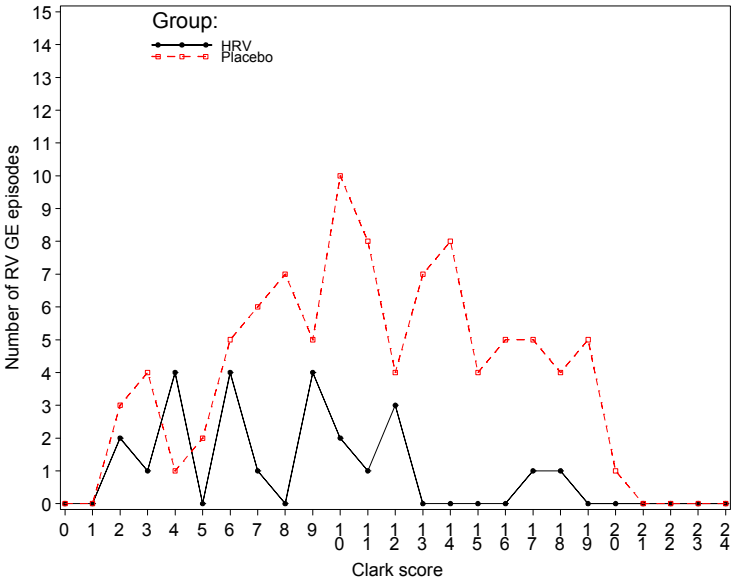
Supplement 90 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5, by severity using the 24-point Clark scale - ATP cohort for efficacy

Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-8)**	461	71.3	252	61.0
	Moderate (9-16)	178	27.5	139	33.7
	Severe (≥17)	5	0.8	21	5.1
	Unknown	3	0.5	1	0.2
	Any	647	100	413	100
RV GE	**Mild (1-8)**	12	50.0	28	29.8
	Moderate (9-16)	10	41.7	51	54.3
	Severe (≥17)	2	8.3	15	16.0
	Any	24	100	94	100

n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported

Any = any specified symptom reported, regardless of Clark severity scale

Supplement 91 Distribution of Clark score for RV GE reported from 2 weeks after Dose 2 up to Visit 5 – ATP cohort for efficacy



Supplement 92 Characteristics (based on Clark scale) of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 24 Value or n	%	Placebo N'= 94 Value or n	%
Severity Score	**Mean**	8.000	-	11.234	-
	SD	4.314	-	4.636	-
	Median	8.0	-	11.0	-
	Minimum	2	-	2	-
	Maximum	18	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	19	79.2	47	50.0
	5-7 days	5	20.8	42	44.7
	> 7 days	0	0.0	5	5.3
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	9	37.5	24	25.5
	5-7	11	45.8	37	39.4
	> 7	4	16.7	33	35.1
Duration of vomiting (days)	**0 - 1 day**	20	83.3	49	52.1
	2 days	3	12.5	22	23.4
	3-5 days	0	0.0	20	21.3
	> 5 days	1	4.2	3	3.2
Maximum number of episodes of Vomiting/24 hours	**0**	13	54.2	18	19.1
	1-3	9	37.5	54	57.4
	4-6	2	8.3	12	12.8
	> 6	0	0.0	10	10.6
Duration of fever (days)	**0 day**	11	45.8	23	24.5
	1-2 day	11	45.8	55	58.5
	3-4 days	2	8.3	16	17.0
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	11	45.8	23	24.5
	38.0-38.2°C	0	0.0	4	4.3
	38.3-38.7°C	4	16.7	20	21.3
	≥ 38.8°C	9	37.5	47	50.0
Duration of behavioral symptoms	**0 day**	7	29.2	20	21.3
	1-2 days	12	50.0	38	40.4
	3-4 days	3	12.5	25	26.6
	≥ 5 days	2	8.3	11	11.7
Behavioral symptoms	**Behave as usual**	7	29.2	20	21.3
	Irritable/less playful	8	33.3	8	8.5
	Lethargic/listless	8	33.3	65	69.1
	Seizures	1	4.2	1	1.1

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 93 Characteristics (based on Clark scale) of RV GE episodes of G1 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 4 Value or n	%	Placebo N'= 45 Value or n	%
Severity Score	Mean	10.250	-	11.133	-
	SD	5.852	-	4.998	-
	Median	10.5	-	11.0	-
	Minimum	3	-	2.	-
	Maximum	17	-	20	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	3	75.0	23	51.1
	5-7 days	1	25.0	20	44.4
	> 7 days	0	0.0	2	4.4
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	2-4	1	25.0	11	24.4
	5-7	2	50.0	19	42.2
	> 7	1	25.0	15	33.3
Duration of vomiting (days)	0 - 1 day	3	75.0	23	51.1
	2 days	1	25.0	10	22.2
	3-5 days	0	0.0	9	20.0
	> 5 days	0	0.0	3	6.7
Maximum number of episodes of Vomiting/24 hours	0	1	25.0	11	24.4
	1-3	2	50.0	22	48.9
	4-6	1	25.0	6	13.3
	> 6	0	0.0	6	13.3
Duration of fever (days)	0 day	1	25.0	13	28.9
	1-2 day	2	50.0	23	51.1
	3-4 days	1	25.0	9	20.0
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	< 38.0°C	1	25.0	13	28.9
	38.0-38.2°C	0	0.0	2	4.4
	38.3-38.7°C	0	0.0	10	22.2
	≥ 38.8°C	3	75.0	20	44.4
Duration of behavioral symptoms	0 day	1	25.0	10	22.2
	1-2 days	1	25.0	16	35.6
	3-4 days	2	50.0	13	28.9
	≥ 5 days	0	0.0	6	13.3
Behavioral symptoms	Behave as usual	1	25.0	10	22.2
	Irritable/less playful	1	25.0	5	11.1
	Lethargic/listless	2	50.0	29	64.4
	Seizures	0	0.0	1	2.2

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 94 Characteristics (based on Clark scale) of RV GE episodes of G9 with no other G type reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 13 Value or n	%	Placebo N'= 27 Value or n	%
Severity Score	Mean	7.538	-	11.667	-
	SD	4.502	-	5.038	-
	Median	6.0	-	13.0	-
	Minimum	2	-	2	-
	Maximum	18	-	19	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	9	69.2	11	40.7
	5-7 days	4	30.8	13	48.1
	> 7 days	0	0.0	3	11.1
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	2-4	4	30.8	4	14.8
	5-7	6	46.2	10	37.0
	> 7	3	23.1	13	48.1
Duration of vomiting (days)	0 - 1 day	12	92.3	13	48.1
	2 days	0	0.0	6	22.2
	3-5 days	0	0.0	8	29.6
	> 5 days	1	7.7	0	0.0
Maximum number of episodes of Vomiting/24 hours	0	8	61.5	3	11.1
	1-3	4	30.8	18	66.7
	4-6	1	7.7	3	11.1
	> 6	0	0.0	3	11.1
Duration of fever (days)	0 day	7	53.8	5	18.5
	1-2 day	6	46.2	17	63.0
	3-4 days	0	0.0	5	18.5
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	< 38.0°C	7	53.8	5	18.5
	38.0-38.2°C	0	0.0	2	7.4
	38.3-38.7°C	3	23.1	8	29.6
	≥ 38.8°C	3	23.1	12	44.4
Duration of behavioral symptoms	0 day	5	38.5	8	29.6
	1-2 days	6	46.2	7	25.9
	3-4 days	0	0.0	9	33.3
	≥ 5 days	2	15.4	3	11.1
Behavioral symptoms	Behave as usual	5	38.5	8	29.6
	Irritable/less playful	3	23.1	2	7.4
	Lethargic/listless	4	30.8	17	63.0
	Seizures	1	7.7	0	0.0

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 95 Characteristics (based on Clark scale) of RV GE episodes of G4 with no other G type reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 3 Value or n	%	Placebo N'= 12 Value or n	%
Severity Score	Mean	8.333	-	11.083	-
	SD	2.082	-	3.370	-
	Median	9.0	-	10.5	-
	Minimum	6	-	6	-
	Maximum	10	-	17	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	3	100	6	50.0
	5-7 days	0	0.0	6	50.0
	> 7 days	0	0.0	0	0.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	2-4	0	0.0	4	33.3
	5-7	3	100	5	41.7
	> 7	0	0.0	3	25.0
Duration of vomiting (days)	0 - 1 day	3	100	7	58.3
	2 days	0	0.0	2	16.7
	3-5 days	0	0.0	3	25.0
	> 5 days	0	0.0	0	0.0
Maximum number of episodes of Vomiting/24 hours	0	2	66.7	2	16.7
	1-3	1	33.3	9	75.0
	4-6	0	0.0	1	8.3
	> 6	0	0.0	0	0.0
Duration of fever (days)	0 day	1	33.3	3	25.0
	1-2 day	1	33.3	8	66.7
	3-4 days	1	33.3	1	8.3
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	< 38.0°C	1	33.3	3	25.0
	38.0-38.2°C	0	0.0	0	0.0
	38.3-38.7°C	1	33.3	2	16.7
	≥ 38.8°C	1	33.3	7	58.3
Duration of behavioral symptoms	0 day	0	0.0	1	8.3
	1-2 days	2	66.7	7	58.3
	3-4 days	1	33.3	3	25.0
	≥ 5 days	0	0.0	1	8.3
Behavioral symptoms	Behave as usual	0	0.0	1	8.3
	Irritable/less playful	3	100	0	0.0
	Lethargic/listless	0	0.0	11	91.7
	Seizures	0	0.0	0	0.0

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 96 Characteristics (based on Clark scale) of all cause GE episodes reported from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 647 Value or n	%	Placebo N'= 413 Value or n	%
Severity Score	**Mean**	6.436	-	7.731	-
	SD	3.725	-	4.657	-
	Median	6.0	-	7.0	-
	Minimum	0	-	0	-
	Maximum	19	-	23	-
Duration of looser than normal stools (days)	**0 day**	4	0.6	2	0.5
	1-4 days	437	67.5	274	66.3
	5-7 days	150	23.2	101	24.5
	> 7 days	56	8.7	36	8.7
Maximum number of looser than normal stools/24 hours	**0**	4	0.6	2	0.5
	2-4	279	43.1	154	37.3
	5-7	268	41.4	164	39.7
	> 7	96	14.8	93	22.5
Duration of vomiting (days)	**0 - 1 day**	554	85.6	303	73.4
	2 days	49	7.6	55	13.3
	3-5 days	36	5.6	49	11.9
	> 5 days	8	1.2	6	1.5
Maximum number of episodes of Vomiting/24 hours	**0**	401	62.0	203	49.2
	1-3	193	29.8	152	36.8
	4-6	37	5.7	34	8.2
	> 6	16	2.5	24	5.8
Duration of fever (days)	**0 day**	454	70.2	243	58.8
	1-2 day	154	23.8	138	33.4
	3-4 days	31	4.8	30	7.3
	≥ 5 days	8	1.2	2	0.5
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	454	70.2	243	58.8
	38.0-38.2°C	44	6.8	25	6.1
	38.3-38.7°C	52	8.0	53	12.8
	≥ 38.8°C	97	15.0	92	22.3
Duration of behavioral symptoms	**0 day**	325	50.2	179	43.3
	1-2 days	217	33.5	141	34.1
	3-4 days	66	10.2	61	14.8
	≥ 5 days	39	6.0	32	7.7
Behavioral symptoms	**Behave as usual**	325	50.2	179	43.3
	Irritable/less playful	110	17.0	60	14.5
	Lethargic/listless	195	30.1	167	40.4
	Seizures	17	2.6	7	1.7

N' = number of all cause 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 97 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	2	0.1	0.0	0.3	93.3	71.0	99.3	<0.001
Placebo	1302	15	1.2	0.6	1.9				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 98 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2572	1	0.0	0.0	0.2	93.7	52.8	99.9	0.001
Placebo	1302	8	0.6	0.3	1.2				
G2									
HRV	2572	0	0.0	0.0	0.1	-	-	-	-
Placebo	1302	0	0.0	0.0	0.3				
G3									
HRV	2572	0	0.0	0.0	0.1	-	-	-	-
Placebo	1302	0	0.0	0.0	0.3				
G4									
HRV	2572	0	0.0	0.0	0.1	100	-1874.3	100	0.336
Placebo	1302	1	0.1	0.0	0.4				
G9									
HRV	2572	1	0.0	0.0	0.2	91.6	30.5	99.8	0.007
Placebo	1302	6	0.5	0.2	1.0				
Pooled Non G1 (G4, G9)									
HRV	2572	1	0.0	0.0	0.2	92.8	43.7	99.8	0.003
Placebo	1302	7	0.5	0.2	1.1				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one specified severe RV GE episode caused by the circulating wild-type RV in each group

95% CI,LL,UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 99 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Clark scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5 - ATP efficacy cohort

Severity using Clark scale	Group	N	n/N n	%	95%CI LL	UL	Vaccine Efficacy %	95%CI LL	UL	P-value
≥17	**HRV**	2572	2	0.1	0.0	0.3	93.3	71.0	99.3	<0.001
	Placebo	1302	15	1.2	0.6	1.9				
≥18	**HRV**	2572	1	0.0	0.0	0.2	94.9	64.4	99.9	<0.001
	Placebo	1302	10	0.8	0.4	1.4				
≥19	**HRV**	2572	0	0.0	0.0	0.1	100	57.0	100	0.001
	Placebo	1302	6	0.5	0.2	1.0				
≥20	**HRV**	2572	0	0.0	0.0	0.1	100	-1874.3	100	0.336
	Placebo	1302	1	0.1	0.0	0.4				
≥21	**HRV**	2572	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1302	0	0.0	0.0	0.3				
≥22	**HRV**	2572	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1302	0	0.0	0.0	0.3				
≥23	**HRV**	2572	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1302	0	0.0	0.0	0.3				
≥24	**HRV**	2572	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1302	0	0.0	0.0	0.3				

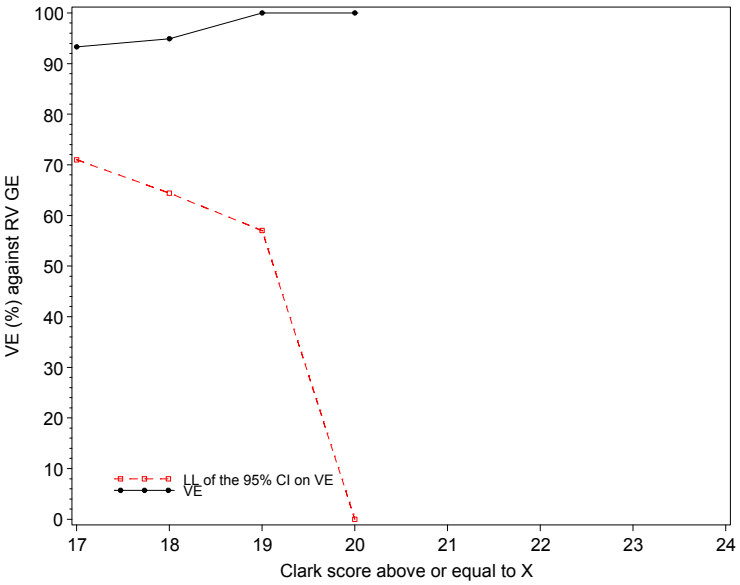
N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Clark scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 100 Efficacy of the vaccine against RV GE episodes with a score greater than or equal to X on the Clark scale from 2 weeks after Dose 2 up to Visit 5 – ATP efficacy cohort



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Supplement 101 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	193	2	1.0	0.1	3.7	74.9	-75.3	97.7	0.099
	Placebo	97	4	4.1	1.1	10.2				
Finland	**HRV**	1893	19	1.0	0.6	1.6	88.6	81.0	93.4	<0.001
	Placebo	956	84	8.8	7.1	10.8				
France	**HRV**	95	2	2.1	0.3	7.4	78.9	-28.6	98.0	0.048
	Placebo	50	5	10.0	3.3	21.8				
Germany	**HRV**	179	1	0.6	0.0	3.1	-infinity	-infinity	98.7	1.000
	Placebo	94	0	0.0	0.0	3.8	-	-	-	-
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	0	0.0	0.0	1.9	100	-1780.7	100	0.325
	Placebo	95	1	1.1	0.0	5.7				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 102 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	193	0	0.0	0.0	1.9	100	-167.6	100	0.111
	Placebo	97	2	2.1	0.3	7.3				
Finland	HRV	1893	4	0.2	0.1	0.5	96.4	90.2	99.1	<0.001
	Placebo	956	56	5.9	4.5	7.5				
France	HRV	95	1	1.1	0.0	5.7	73.7	-405.5	99.6	0.273
	Placebo	50	2	4.0	0.5	13.7				
Germany	HRV	179	0	0.0	0.0	2.0	-	-	-	-
	Placebo	94	0	0.0	0.0	3.8				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	197	0	0.0	0.0	1.9	-	-	-	-
	Placebo	95	0	0.0	0.0	3.8				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 103 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	193	0	0.0	0.0	1.9	-	-	-	-
	Placebo	97	0	0.0	0.0	3.7				
Finland	HRV	1893	2	0.1	0.0	0.4	92.8	68.6	99.2	<0.001
	Placebo	956	14	1.5	0.8	2.4				
France	HRV	95	0	0.0	0.0	3.8	100	-1952.6	100	0.345
	Placebo	50	1	2.0	0.1	10.6				
Germany	HRV	179	0	0.0	0.0	2.0	-	-	-	-
	Placebo	94	0	0.0	0.0	3.8				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	197	0	0.0	0.0	1.9	-	-	-	-
	Placebo	95	0	0.0	0.0	3.8				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 104 Percentage of subjects reporting all cause GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	193	38	19.7	14.3	26.0	-0.5	-84.6	43.5	1.000
	Placebo	97	19	19.6	12.2	28.9				
Finland	**HRV**	1893	456	24.1	22.2	26.1	18.0	4.6	29.5	0.002
	Placebo	956	281	29.4	26.5	32.4				
France	**HRV**	95	18	18.9	11.6	28.3	36.8	-34.6	69.9	0.148
	Placebo	50	15	30.0	17.9	44.6				
Germany	**HRV**	179	16	8.9	5.2	14.1	16.0	-107.1	64.2	0.668
	Placebo	94	10	10.6	5.2	18.7				
Italy	**HRV**	15	3	20.0	4.3	48.1	-infinity	-infinity	72.5	0.250
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	28	14.2	9.7	19.9	3.6	-98.2	50.9	1.000
	Placebo	95	14	14.7	8.3	23.5				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 105 Percentage of subjects reporting all cause severe (Vesikari scale) GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	193	9	4.7	2.2	8.7	-13.1	-402.5	68.4	1.000
	Placebo	97	4	4.1	1.1	10.2				
Finland	HRV	1893	96	5.1	4.1	6.2	56.7	42.6	67.4	<0.001
	Placebo	956	112	11.7	9.7	13.9				
France	HRV	95	3	3.2	0.7	9.0	47.4	-293.0	93.0	0.415
	Placebo	50	3	6.0	1.3	16.5				
Germany	HRV	179	1	0.6	0.0	3.1	47.5	-4022.2	99.3	1.000
	Placebo	94	1	1.1	0.0	5.8				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	197	7	3.6	1.4	7.2	-12.5	-574.3	74.3	1.000
	Placebo	95	3	3.2	0.7	9.0				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 106 Percentage of subjects reporting any RV GE episodes with medical attention and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	193	2	1.0	0.1	3.7	74.9	-75.3	97.7	0.099
	Placebo	97	4	4.1	1.1	10.2				
Finland	HRV	1893	5	0.3	0.1	0.6	95.2	88.2	98.5	<0.001
	Placebo	956	53	5.5	4.2	7.2				
France	HRV	95	2	2.1	0.3	7.4	73.7	-83.6	97.6	0.182
	Placebo	50	4	8.0	2.2	19.2				
Germany	HRV	179	1	0.6	0.0	3.1	-infinity	-infinity	98.7	1.000
	Placebo	94	0	0.0	0.0	3.8				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	197	0	0.0	0.0	1.9	100	-1780.7	100	0.325
	Placebo	95	1	1.1	0.0	5.7				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with medical attention in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 107 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 up to Visit 5 – Total vaccinated cohort

			n/N		
				95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**
HRV	2646	5*	0.2	0.1	0.4
Placebo	1348	0	0.0	0.0	0.3

N = number of subjects included in each group
n/% = number/percentage of subjects with vaccine virus in at least one stool sample collected in case of GE episode
95% CI = exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
*four episodes of G1/P8 vaccine strain and one episode of G1/P8 vaccine strain with G9/P8 wild type

Supplement 108 Percentage of subjects who reported GE episodes and RV GE episodes from Dose 1 up to Visit 5 - Total vaccinated cohort

Event	Total number of episode reported	HRV N= 2646 n	%	Placebo N= 1348 n	%
GE	**1**	584	22.1	344	25.5
	2	114	4.3	67	5.0
	3	18	0.7	16	1.2
	4	6	0.2	5	0.4
	5	2	0.1	0	0.0
	Any	724	27.4	432	32.0
RV GE	**1**	26	1.0	104	7.7
	Any	26	1.0	104	7.7

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 episode

Supplement 109 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 5 - Total vaccinated cohort

Category	HRV N'= 900 n	%	Placebo N'= 546 n	%
No stools collected	73	8.1	48	8.8
Stools collected but no results available*	17	1.9	13	2.4
No stool results available	90	10.0	61	11.2

N' = number of GE episodes reported

n/% = number/percentage of GE episodes within the specified category

* = due to quantity not sufficient or stool sample not tested

Supplement 110 Number of GE episodes and RV GE episodes reported from Dose 1 up to Visit 5, by severity using the 20-point Vesikari scale - Total vaccinated cohort

Event	Severity using Vesikari scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-6)**	477	53.0	231	42.3
	Moderate (7-10)	283	31.4	164	30.0
	Severe (≥11)	137	15.2	148	27.1
	Unknown	3	0.3	3	0.5
	Any	900	100	546	100
RV GE	**Mild (1-6)**	9	34.6	12	11.5
	Moderate (7-10)	12	46.2	28	26.9
	Severe (≥11)	5	19.2	64	61.5
	Any	26	100	104	100

n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported

Any = any specified symptom reported, regardless of Vesikari severity scale

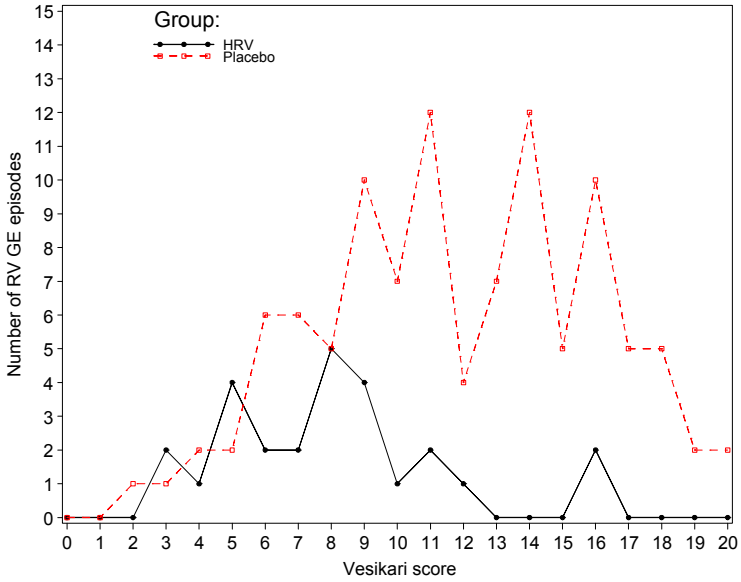
Supplement 111 Number of GE episodes and RV GE episodes reported from Dose 1 up to Visit 5, by severity using the 24-point Clark scale - Total vaccinated cohort

Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-8)**	673	74.8	350	64.1
	Moderate (9-16)	217	24.1	170	31.1
	Severe (≥17)	5	0.6	21	3.8
	Unknown	5	0.6	5	0.9
	Any	900	100	546	100
RV GE	**Mild (1-8)**	13	50.0	30	28.8
	Moderate (9-16)	11	42.3	59	56.7
	Severe (≥17)	2	7.7	15	14.4
	Any	26	100	104	100

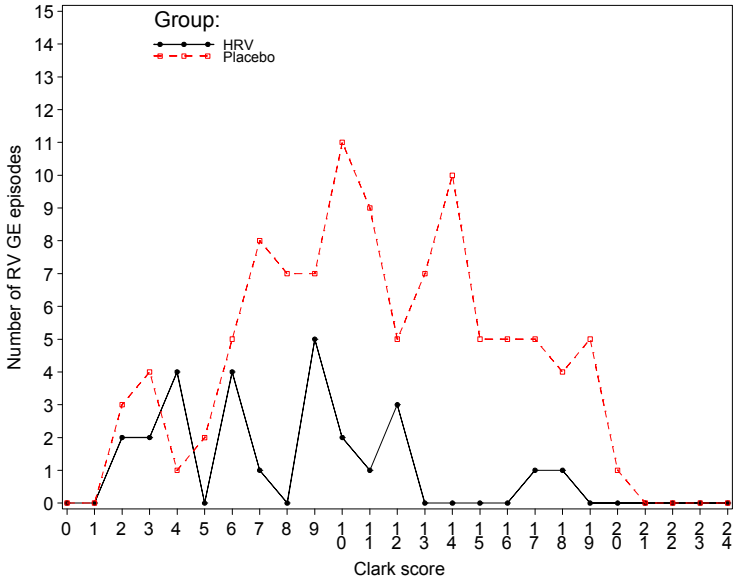
n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported

Any = any specified symptom reported, regardless of Clark severity scale

Supplement 112 Distribution of Vesikari score for RV GE reported from Dose 1 up to Visit 5 – Total vaccinated cohort



Supplement 113 Distribution of Clark score for RV GE reported from Dose 1 up to Visit 5 – Total vaccinated cohort



Supplement 114 Percentage of subjects with RV GE episodes reported from Dose 1 up to Visit 5, by G serotype and P genotype - Total vaccinated cohort

Serotype	HRV N= 2646		Placebo N= 1348	
	n	%	n	%
Any	26	1.0	104	7.7
G1 wild type	4	0.2	48	3.6
G2	3	0.1	4	0.3
G3	2	0.1	7	0.5
G4	3	0.1	14	1.0
G9	14	0.5	32	2.4
P4	3	0.1	3	0.2
P8 wild type	23	0.9	100	7.4
Unknown P type*	0	0.0	1	0.1

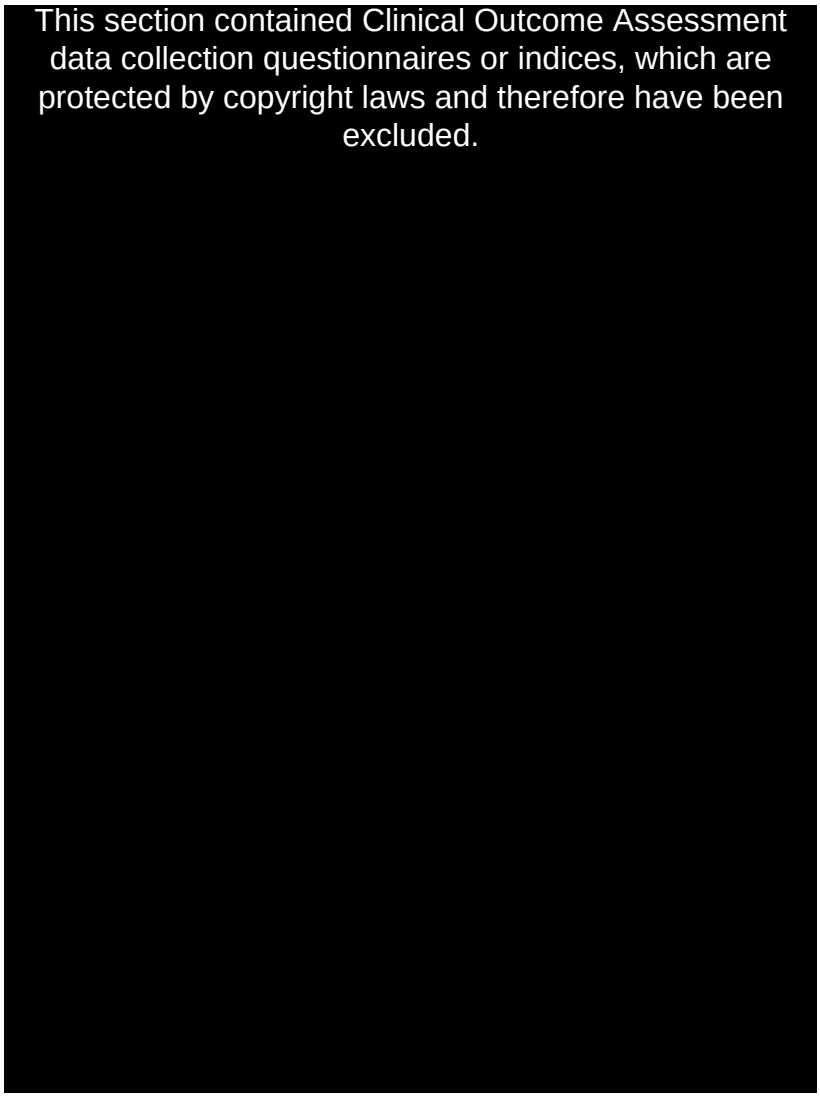
N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype in each group
Any = number of subjects reporting at least one RV GE episode, whatever the serotype
* = not typable

Supplement 115 Number of RV GE episodes reported from Dose 1 up to Visit 5, by G serotype and P genotype - Total vaccinated cohort

Country	Serotype	HRV N'= 26 n	%	Placebo N'= 104 N	%
Czech Republic	**G9 and P8wt**	0	0.0	1	25.0
	G2 and P4	1	50.0	0	0.0
	G1wt and P8wt	0	0.0	3	75.0
	G4 and P8 wt	1	50.0	0	0.0
Finland	**G2 and unknown P type**	0	0.0	1	1.1
	G9 and P8wt	13	50.0	24	27.3
	G2 and P4	2	10.0	3	3.4
	G1w and G4 and P8wt	0	0.0	1	1.1
	G1wt and P8wt	3	15.0	42	47.7
	G3 and P8wt	1	5.0	5	5.7
	G4 and P8wt	1	5.0	12	13.6
France	**G9 and P8wt**	1	50.0	4	80.0
	G1wt and P8wt	1	50.0	1	20.0
Germany	**G1wt and P8wt**	0	0.0	1	100
	G4 and P8wt	1	100	0	0.0
Spain	**G9 and P8wt**	0	0.0	3	50.0
	G3 and P8wt	1	100	2	33.3
	G4 and P8wt	0	0.0	1	16.7

N' = number of RV GE episodes reported
n/% = number/percentage of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type

Supplement 116 Characteristics (based on Vesikari scale) of RV GE episodes reported from Dose 1 up to Visit 5 - Total vaccinated cohort



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 117 Characteristics (based on Vesikari scale) of RV GE episodes of G1 wild type with no other G type reported from Dose 1 up to Visit 5 - Total vaccinated cohort

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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 118 Characteristics (based on Vesikari scale) of RV GE episodes of G9 with no other G type reported from Dose 1 up to Visit 5 - Total vaccinated cohort

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 119 Characteristics (based on Vesikari scale) of RV GE episodes of G4 with no other G type reported from Dose 1 up to Visit 5 - Total vaccinated cohort

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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 120 Characteristics (based on Vesikari scale) of all cause GE episodes reported from Dose 1 up to Visit 5 - Total vaccinated cohort

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

N' = number of all cause 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 121 Characteristics (based on Clark scale) of RV GE episodes reported from Dose 1 up to Visit 5 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 26 Value or n	%	Placebo N'= 104 Value or n	%
Severity Score	**Mean**	7.846	-	11.192	-
	SD	4.259	-	4.490	-
	Median	8.0	-	11.0	-
	Minimum	2	-	2	-
	Maximum	18	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	21	80.8	51	49.0
	5-7 days	5	19.2	48	46.2
	> 7 days	0	0.0	5	4.8
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	9	34.6	26	25.0
	5-7	13	50.0	40	38.5
	> 7	4	15.4	38	36.5
Duration of vomiting (days)	**0 - 1 day**	22	84.6	58	55.8
	2 days	3	11.5	23	22.1
	3-5 days	0	0.0	20	19.2
	> 5 days	1	3.8	3	2.9
Maximum number of episodes of Vomiting/24 hours	**0**	15	57.7	22	21.2
	1-3	9	34.6	58	55.8
	4-6	2	7.7	14	13.5
	> 6	0	0.0	10	9.6
Duration of fever (days)	**0 day**	12	46.2	26	25.0
	1-2 day	12	46.2	62	59.6
	3-4 days	2	7.7	16	15.4
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	12	46.2	26	25.0
	38.0-38.2°C	0	0.0	5	4.8
	38.3-38.7°C	5	19.2	22	21.2
	≥ 38.8°C	9	34.6	51	49.0
Duration of behavioral symptoms	**0 day**	8	30.8	20	19.2
	1-2 days	12	46.2	42	40.4
	3-4 days	4	15.4	29	27.9
	≥ 5 days	2	7.7	13	12.5
Behavioral symptoms	**Behave as usual**	8	30.8	20	19.2
	Irritable/less playful	9	34.6	10	9.6
	Lethargic/listless	8	30.8	73	70.2
	Seizures	1	3.8	1	1.0

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 122 Characteristics (based on Clark scale) of RV GE episodes of G1 wild type with no other G type reported from Dose 1 up to Visit 5 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 4 Value or n	%	Placebo N'= 47 Value or n	%
Severity Score	Mean	10.250	-	11.106	-
	SD	5.852	-	4.944	-
	Median	10.5	-	11.0	-
	Minimum	3	-	2	-
	Maximum	17	-	20	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	3	75.0	24	51.1
	5-7 days	1	25.0	21	44.7
	> 7 days	0	0.0	2	4.3
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	2-4	1	25.0	11	23.4
	5-7	2	50.0	20	42.6
	> 7	1	25.0	16	34.0
Duration of vomiting (days)	0 - 1 day	3	75.0	25	53.2
	2 days	1	25.0	10	21.3
	3-5 days	0	0.0	9	19.1
	> 5 days	0	0.0	3	6.4
Maximum number of episodes of Vomiting/24 hours	0	1	25.0	12	25.5
	1-3	2	50.0	23	48.9
	4-6	1	25.0	6	12.8
	> 6	0	0.0	6	12.8
Duration of fever (days)	0 day	1	25.0	14	29.8
	1-2 day	2	50.0	24	51.1
	3-4 days	1	25.0	9	19.1
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	< 38.0°C	1	25.0	14	29.8
	38.0-38.2°C	0	0.0	2	4.3
	38.3-38.7°C	0	0.0	11	23.4
	≥ 38.8°C	3	75.0	20	42.6
Duration of behavioral symptoms	0 day	1	25.0	10	21.3
	1-2 days	1	25.0	16	34.0
	3-4 days	2	50.0	14	29.8
	≥ 5 days	0	0.0	7	14.9
Behavioral symptoms	Behave as usual	1	25.0	10	21.3
	Irritable/less playful	1	25.0	5	10.6
	Lethargic/listless	2	50.0	31	66.0
	Seizures	0	0.0	1	2.1

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 123 Characteristics (based on Clark scale) of RV GE episodes of G9 with no other G type reported from Dose 1 up to Visit 5 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 13 Value or n	%	Placebo N'= 32 Value or n	%
Severity Score	Mean	7.538	-	11.625	-
	SD	4.502	-	4.689	-
	Median	6.0	-	12.0	-
	Minimum	2	-	2	-
	Maximum	18	-	19	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	9	69.2	13	40.6
	5-7 days	4	30.8	16	50.0
	> 7 days	0	0.0	3	9.4
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	2-4	4	30.8	5	15.6
	5-7	6	46.2	12	37.5
	> 7	3	23.1	15	46.9
Duration of vomiting (days)	0 - 1 day	12	92.3	17	53.1
	2 days	0	0.0	7	21.9
	3-5 days	0	0.0	8	25.0
	> 5 days	1	7.7	0	0.0
Maximum number of episodes of Vomiting/24 hours	0	8	61.5	4	12.5
	1-3	4	30.8	20	62.5
	4-6	1	7.7	5	15.6
	> 6	0	0.0	3	9.4
Duration of fever (days)	0 day	7	53.8	6	18.8
	1-2 day	6	46.2	21	65.6
	3-4 days	0	0.0	5	15.6
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	< 38.0°C	7	53.8	6	18.8
	38.0-38.2°C	0	0.0	2	6.3
	38.3-38.7°C	3	23.1	9	28.1
	≥ 38.8°C	3	23.1	15	46.9
Duration of behavioral symptoms	0 day	5	38.5	8	25.0
	1-2 days	6	46.2	10	31.3
	3-4 days	0	0.0	10	31.3
	≥ 5 days	2	15.4	4	12.5
Behavioral symptoms	Behave as usual	5	38.5	8	25.0
	Irritable/less playful	3	23.1	4	12.5
	Lethargic/listless	4	30.8	20	62.5
	Seizures	1	7.7	0	0.0

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 124 Characteristics (based on Clark scale) of RV GE episodes of G4 with no other G type reported from Dose 1 up to Visit 5 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 3 Value or n	%	Placebo N'= 13 Value or n	%
Severity Score	Mean	8.333	-	10.769	-
	SD	2.082	-	3.419	-
	Median	9.0	-	10.0	-
	Minimum	6	-	6	-
	Maximum	10	-	17	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	3	100	7	53.8
	5-7 days	0	0.0	6	46.2
	> 7 days	0	0.0	0	0.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	2-4	0	0.0	5	38.5
	5-7	3	100	5	38.5
	> 7	0	0.0	3	23.1
Duration of vomiting (days)	0 - 1 day	3	100	8	61.5
	2 days	0	0.0	2	15.4
	3-5 days	0	0.0	3	23.1
	> 5 days	0	0.0	0	0.0
Maximum number of episodes of Vomiting/24 hours	0	2	66.7	3	23.1
	1-3	1	33.3	9	69.2
	4-6	0	0.0	1	7.7
	> 6	0	0.0	0	0.0
Duration of fever (days)	0 day	1	33.3	3	23.1
	1-2 day	1	33.3	9	69.2
	3-4 days	1	33.3	1	7.7
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	< 38.0°C	1	33.3	3	23.1
	38.0-38.2°C	0	0.0	1	7.7
	38.3-38.7°C	1	33.3	2	15.4
	≥ 38.8°C	1	33.3	7	53.8
Duration of behavioral symptoms	0 day	0	0.0	1	7.7
	1-2 days	2	66.7	8	61.5
	3-4 days	1	33.3	3	23.1
	≥ 5 days	0	0.0	1	7.7
Behavioral symptoms	Behave as usual	0	0.0	1	7.7
	Irritable/less playful	3	100	0	0.0
	Lethargic/listless	0	0.0	12	92.3
	Seizures	0	0.0	0	0.0

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 125 Characteristics (based on Clark scale) of all cause GE episodes reported from Dose 1 up to Visit 5 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 900 Value or n	%	Placebo N'= 546 Value or n	%
Severity Score	**Mean**	6.092	-	7.262	-
	SD	3.605	-	4.433	-
	Median	5.0	-	6.0	-
	Minimum	0	-	0	-
	Maximum	19	-	23	-
Duration of looser than normal stools (days)	**0 day**	7	0.8	6	1.1
	1-4 days	616	68.4	354	64.8
	5-7 days	191	21.2	132	24.2
	> 7 days	86	9.6	54	9.9
Maximum number of looser than normal stools/24 hours	**0**	7	0.8	6	1.1
	2-4	392	43.6	207	37.9
	5-7	377	41.9	224	41.0
	> 7	124	13.8	109	20.0
Duration of vomiting (days)	**0 - 1 day**	794	88.2	425	77.8
	2 days	54	6.0	64	11.7
	3-5 days	42	4.7	51	9.3
	> 5 days	10	1.1	6	1.1
Maximum number of episodes of Vomiting/24 hours	**0**	617	68.6	304	55.7
	1-3	219	24.3	179	32.8
	4-6	44	4.9	39	7.1
	> 6	20	2.2	24	4.4
Duration of fever (days)	**0 day**	663	73.7	352	64.5
	1-2 day	192	21.3	160	29.3
	3-4 days	37	4.1	32	5.9
	≥ 5 days	8	0.9	2	0.4
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	663	73.7	352	64.5
	38.0-38.2°C	57	6.3	29	5.3
	38.3-38.7°C	63	7.0	61	11.2
	≥ 38.8°C	117	13.0	104	19.0
Duration of behavioral symptoms	**0 day**	463	51.4	238	43.6
	1-2 days	304	33.8	189	34.6
	3-4 days	86	9.6	78	14.3
	≥ 5 days	47	5.2	41	7.5
Behavioral symptoms	**Behave as usual**	463	51.4	238	43.6
	Irritable/less playful	160	17.8	94	17.2
	Lethargic/listless	258	28.7	207	37.9
	Seizures	19	2.1	7	1.3

N' = number of all cause 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 126 Duration (in years) of the follow-up period from Dose 1 up Visit 5 - Total vaccinated cohort

Duration (years) of follow-up period	HRV N= 2646	Placebo N= 1348
Total	1759.8	902.5
Mean	0.665	0.670
SD	0.109	0.105
Minimum	0.025	0.079
Q1	0.595	0.604
Median	0.701	0.707
Q3	0.748	0.745
Maximum	0.860	0.882

N = number of subjects included in each group
Total = sum of follow-up period expressed in year
SD = standard deviation
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 127 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	26	1.0	0.6	1.4	87.3	80.3	92.0	<0.001
Placebo	1348	104	7.7	6.3	9.3				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 128 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by country - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	2	1.0	0.1	3.6	74.9	-75.3	97.7	0.099
	Placebo	100	4	4.0	1.1	9.9				
Finland	**HRV**	1918	20	1.0	0.6	1.6	88.5	81.1	93.3	<0.001
	Placebo	972	88	9.1	7.3	11.0				
France	**HRV**	95	2	2.1	0.3	7.4	78.5	-31.2	98.0	0.051
	Placebo	51	5	9.8	3.3	21.4				
Germany	**HRV**	190	1	0.5	0.0	2.9	47.9	-3990.1	99.3	1.000
	Placebo	99	1	1.0	0.0	5.5				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	1	0.4	0.0	2.4	91.6	30.4	99.8	0.007
	Placebo	116	6	5.2	1.9	10.9				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 129 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 1, by RV serotype - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2646	4	0.2	0.0	0.4	95.8	88.4	98.9	<0.001
Placebo	1348	48	3.6	2.6	4.7				
G2									
HRV	2646	3	0.1	0.0	0.3	61.8	-125.9	94.4	0.235
Placebo	1348	4	0.3	0.1	0.8				
G3									
HRV	2646	2	0.1	0.0	0.3	85.4	23.6	98.5	0.009
Placebo	1348	7	0.5	0.2	1.1				
G4									
HRV	2646	3	0.1	0.0	0.3	89.1	60.9	98.0	<0.001
Placebo	1348	14	1.0	0.6	1.7				
G9									
HRV	2646	14	0.5	0.3	0.9	77.7	57.0	89.0	<0.001
Placebo	1348	32	2.4	1.6	3.3	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)									
HRV	2646	22	0.8	0.5	1.3	80.3	67.3	88.6	<0.001
Placebo	1348	57	4.2	3.2	5.4				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one specified RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 130 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	5	0.2	0.1	0.4	96.0	90.2	98.8	<0.001
Placebo	1348	64	4.7	3.7	6.0				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 131 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by country - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	199	0	0.0	0.0	1.8	100	-167.6	100	0.111
	Placebo	100	2	2.0	0.2	7.0				
Finland	HRV	1918	4	0.2	0.1	0.5	96.4	90.4	99.1	<0.001
	Placebo	972	57	5.9	4.5	7.5		-	-	-
France	HRV	95	1	1.1	0.0	5.7	73.2	-415.6	99.5	0.279
	Placebo	51	2	3.9	0.5	13.5		-	-	-
Germany	HRV	190	0	0.0	0.0	1.9	-	-	-	-
	Placebo	99	0	0.0	0.0	3.7				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	229	0	0.0	0.0	1.6	100	-22.6	100	0.037
	Placebo	116	3	2.6	0.5	7.4				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 132 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by RV serotype - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2646	2	0.1	0.0	0.3	96.5	86.1	99.6	<0.001
Placebo	1348	29	2.2	1.4	3.1				
G2									
HRV	2646	1	0.0	0.0	0.2	74.5	-389.3	99.6	0.265
Placebo	1348	2	0.1	0.0	0.5				
G3									
HRV	2646	0	0.0	0.0	0.1	100	56.7	100	0.001
Placebo	1348	6	0.4	0.2	1.0				
G4									
HRV	2646	0	0.0	0.0	0.1	100	64.7	100	<0.001
Placebo	1348	7	0.5	0.2	1.1				
G9									
HRV	2646	2	0.1	0.0	0.3	95.1	80.2	99.4	<0.001
Placebo	1348	21	1.6	1.0	2.4				
Pooled Non G1 (G2, G3, G4, G9)									
HRV	2646	3	0.1	0.0	0.3	95.8	86.6	99.2	<0.001
Placebo	1348	36	2.7	1.9	3.7				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one specified severe RV GE episode caused by the circulating wild-type RV in each group

95% CI,LL,UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 133 Percentage of subjects reporting severe (Clark score greater than >16) RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	2	0.1	0.0	0.3	93.2	70.8	99.2	<0.001
Placebo	1348	15	1.1	0.6	1.8	-	-	-	-

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 134 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by country - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	0	0.0	0.0	1.8	-	-	-	-
	Placebo	100	0	0.0	0.0	3.6				
Finland	**HRV**	1918	2	0.1	0.0	0.4	92.8	68.5	99.2	<0.001
	Placebo	972	14	1.4	0.8	2.4				
France	**HRV**	95	0	0.0	0.0	3.8	100	-1993.7	100	0.349
	Placebo	51	1	2.0	0.0	10.4				
Germany	**HRV**	190	0	0.0	0.0	1.9	-	-	-	-
	Placebo	99	0	0.0	0.0	3.7				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	0	0.0	0.0	1.6	-	-	-	-
	Placebo	116	0	0.0	0.0	3.1				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 135 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by RV serotype - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2646	1	0.0	0.0	0.2	93.6	52.5	99.9	0.001
Placebo	1348	8	0.6	0.3	1.2				
G2									
HRV	2646	0	0.0	0.0	0.1	-	-	-	-
Placebo	1348	0	0.0	0.0	0.3				
G3									
HRV	2646	0	0.0	0.0	0.1	-	-	-	-
Placebo	1348	0	0.0	0.0	0.3				
G4									
HRV	2646	0	0.0	0.0	0.1	100	-1886.8	100	0.338
Placebo	1348	1	0.1	0.0	0.4				
G9									
HRV	2646	1	0.0	0.0	0.2	91.5	30.0	99.8	0.007
Placebo	1348	6	0.4	0.2	1.0				
Pooled Non G1 (G4, G9)									
HRV	2646	1	0.0	0.0	0.2	92.7	43.4	99.8	0.003
Placebo	1348	7	0.5	0.2	1.1				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one specified RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 136 Percentage of subjects reporting all cause GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by country and for all countries - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	54	27.1	21.1	33.9	-4.4	-73.6	35.8	0.890
	Placebo	100	26	26.0	17.7	35.7				
Finland	**HRV**	1918	569	29.7	27.6	31.8	15.4	3.0	26.2	0.003
	Placebo	972	341	35.1	32.1	38.2				
France	**HRV**	95	26	27.4	18.7	37.5	17.9	-61.3	57.1	0.454
	Placebo	51	17	33.3	20.8	47.9				
Germany	**HRV**	190	22	11.6	7.4	17.0	18.1	-73.0	59.9	0.575
	Placebo	99	14	14.1	8.0	22.6				
Italy	**HRV**	15	3	20.0	4.3	48.1	-infinity	-infinity	72.5	0.250
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	50	21.8	16.7	27.8	25.5	-18.8	52.8	0.144
	Placebo	116	34	29.3	21.2	38.5				
All countries	**HRV**	2646	724	27.4	25.7	29.1	14.6	3.6	24.3	0.002
	Placebo	1348	432	32.0	29.6	34.6				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 137 Percentage of subjects reporting all cause severe (Vesikari scale) GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5, by country and for all countries - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	10	5.0	2.4	9.0	-0.5	-274.7	68.7	1.000
	Placebo	100	5	5.0	1.6	11.3				
Finland	**HRV**	1918	106	5.5	4.5	6.6	54.1	39.8	65.0	<0.001
	Placebo	972	117	12.0	10.1	14.2				
France	**HRV**	95	3	3.2	0.7	9.0	59.7	-138.0	94.1	0.239
	Placebo	51	4	7.8	2.2	18.9				
Germany	**HRV**	190	1	0.5	0.0	2.9	73.9	-400.4	99.6	0.271
	Placebo	99	2	2.0	0.2	7.1				-
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	9	3.9	1.8	7.3	54.4	-24.8	83.6	0.083
	Placebo	116	10	8.6	4.2	15.3				
All countries	**HRV**	2646	129	4.9	4.1	5.8	52.4	39.0	62.8	<0.001
	Placebo	1348	138	10.2	8.7	12.0				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 138 Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	0	0.0	0.0	0.1	100	81.7	100	<0.001
Placebo	1348	12	0.9	0.5	1.5	-	-	-	-

N = number of subjects included in each group

n/% = number/percentage of subjects hospitalized due to RV GE episode caused by the circulating wild-type RV

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 139 Percentage of subjects hospitalized due to GE episodes and efficacy of the vaccine from Dose 1 up to Visit 5 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	12	0.5	0.2	0.8	75.5	49.5	88.8	<0.001
Placebo	1348	25	1.9	1.2	2.7				

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized due to GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 140 Percentage of subjects reporting any RV GE episodes with medical attention and efficacy of the vaccine from Dose 1 up to Visit 5, by country and for all countries - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	2	1.0	0.1	3.6	74.9	-75.3	97.7	0.099
	Placebo	100	4	4.0	1.1	9.9				
Finland	**HRV**	1918	5	0.3	0.1	0.6	95.4	88.6	98.6	<0.001
	Placebo	972	55	5.7	4.3	7.3				
France	**HRV**	95	2	2.1	0.3	7.4	73.2	-87.3	97.6	0.184
	Placebo	51	4	7.8	2.2	18.9				
Germany	**HRV**	190	1	0.5	0.0	2.9	47.9	-3990.1	99.3	1.000
	Placebo	99	1	1.0	0.0	5.5				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	1	0.4	0.0	2.4	91.6	30.4	99.8	0.007
	Placebo	116	6	5.2	1.9	10.9				
All countries	**HRV**	2646	11	0.4	0.2	0.7	92.0	84.8	96.2	<0.001
	Placebo	1348	70	5.2	4.1	6.5				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with medical attention in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 141 Percentage of subjects who reported GE episodes and RV GE episodes from Dose 1 up to 14 days post Dose 2 - Total vaccinated cohort

Event	Total number of episode reported	HRV N= 2646 n	%	Placebo N= 1348 n	%
GE	**1**	200	7.6	116	8.6
	2	16	0.6	6	0.4
	3	4	0.2	0	0.0
	Any	220	8.3	122	9.1
RV GE	**1**	2	0.1	8	0.6
	Any	2	0.1	8	0.6

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 episode

Supplement 142 Percentage of GE episodes with no available stool results from Dose 1 up to 14 days post Dose 2 – Total vaccinated cohort

Category	HRV N'= 244 n	%	Placebo N'= 128 n	%
No stools collected	29	11.9	14	10.9
Stools collected but no results available*	5	2.0	3	2.3
No stool results available	34	13.9	17	13.3

N' = number of GE episodes reported

n/% = number/percentage of GE episodes within the specified category

* = due to quantity not sufficient or stool sample not tested

Supplement 143 Number of GE episodes and RV GE episodes reported from Dose 1 up to 14 days post Dose 2, by severity using the 20-point Vesikari scale - Total vaccinated cohort

Event	Severity using Vesikari scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-6)**	170	69.7	72	56.3
	Moderate (7-10)	57	23.4	39	30.5
	Severe (≥11)	17	7.0	14	10.9
	Unknown	0	0.0	3	2.3
	Any	244	100	128	100
RV GE	**Mild (1-6)**	1	50.0	1	12.5
	Moderate (7-10)	1	50.0	4	50.0
	Severe (≥11)	0	0.0	3	37.5
	Any	2	100	8	100

n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported

Any = any specified symptom reported, regardless of Vesikari severity scale

Supplement 144 Number of GE episodes and RV GE episodes reported from Dose 1 up to 14 days post Dose 2, by severity using the 24-point Clark scale - Total vaccinated cohort

Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-8)**	205	84.0	95	74.2
	Moderate (9-16)	39	16.0	29	22.7
	Severe (≥17)	0	0.0	0	0.0
	Unknown	0	0.0	4	3.1
	Any	244	100	128	100
RV GE	**Mild (1-8)**	1	50.0	1	12.5
	Moderate (9-16)	1	50.0	7	87.5
	Severe (≥17)	0	0.0	0	0.0
	Any	2	100	8	100

n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported

Any = any specified symptom reported, regardless of Vesikari severity scale

Supplement 145 Percentage of subjects with RV GE episodes reported from Dose 1 up to 14 days post Dose 2, by G serotype and P genotype - Total vaccinated cohort

Serotype	HRV N= 2646		Placebo N= 1348	
	n	%	n	%
Any	2	0.1	8	0.6
G1 wild type	0	0.0	1	0.1
G3	1	0.0	2	0.1
G9	1	0.0	5	0.4
P8 wild type	2	0.1	8	0.6

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 146 Number of RV GE episodes reported from Dose 1 up to 14 days post Dose 2, by G serotype and P genotype - Total vaccinated cohort

Country	Serotype	HRV N'= 2 n	%	Placebo N'= 8 N	%
Finland	**G9 and P8wt**	1	100	2	100
Germany	**G1wt and P8wt**	0	0.0	1	100
Spain	**G9 and P8wt**	0	0.0	3	60.0
	G3 and P8wt	1	100	2	40.0
All countries	**G9 and P8wt**	1	50.0	5	62.5
	G1wt and P8wt	0	0.0	1	12.5
	G3 and P8wt	1	50.0	2	25.0

N' = number of RV GE episodes reported
n/% = number/percentage of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type

Supplement 147 Duration (in years) of the follow-up period from Dose 1 up to 14 days post Dose 2 - Total vaccinated cohort

Duration (years) of follow-up period	HRV N= 2646	Placebo N= 1348
Total	526.5	268.1
Mean	0.199	0.199
SD	0.043	0.043
Minimum	0.025	0.079
Q1	0.181	0.181
Median	0.208	0.205
Q3	0.219	0.219
Maximum	0.745	0.882

N = number of subjects included in each group
Total = sum of follow-up period expressed in year
SD = standard deviation
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 148 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from Dose 1 up to 14 days post Dose 2 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	2	0.1	0.0	0.3	87.3	36.2	98.7	0.004
Placebo	1348	8	0.6	0.3	1.2				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 149 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and efficacy of the vaccine from Dose 1 up to 14 days post Dose 2 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	0	0.0	0.0	0.1	100	-23.3	100	0.038
Placebo	1348	3	0.2	0.0	0.6				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 150 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from Dose 1 up to 14 days post Dose 2 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	0	0.0	0.0	0.1	-	-	-	-
Placebo	1348	0	0.0	0.0	0.3				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 151 Percentage of subjects who reported GE episodes and RV GE episodes from Dose 1 up to before Dose 2 - Total vaccinated cohort

Event	Total number of episode reported	HRV N= 2646 n	%	Placebo N= 1348 n	%
GE	**1**	161	6.1	90	6.7
	2	13	0.5	2	0.1
	3	1	0.0	0	0.0
	Any	175	6.6	92	6.8
RV GE	**1**	1	0.0	5	0.4
	Any	1	0.0	5	0.4

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 episode

Supplement 152 Percentage of GE episodes with no available stool results from Dose 1 up to before Dose 2 – Total vaccinated cohort

Category	HRV N'= 190 n	%	Placebo N'= 94 n	%
No stools collected	24	12.6	13	13.8
Stools collected but no results available*	4	2.1	1	1.1
No stool results available	28	14.7	14	14.9

N' = number of GE episodes reported

n/% = number/percentage of GE episodes within the specified category

* = due to quantity not sufficient or stool sample not tested

Supplement 153 Number of GE episodes and RV GE episodes reported from Dose 1 up to before Dose 2, by severity using the 20-point Vesikari scale - Total vaccinated cohort

Event	Severity using Vesikari scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-6)**	134	70.5	53	56.4
	Moderate (7-10)	43	22.6	29	30.9
	Severe (≥11)	13	6.8	9	9.6
	Unknown	0	0.0	3	3.2
	Any	190	100	94	100
RV GE	**Mild (1-6)**	0	0.0	0	0.0
	Moderate (7-10)	1	100	2	40.0
	Severe (≥11)	0	0.0	3	60.0
	Any	1	100	5	100

n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported

Any = any specified symptom reported, regardless of Vesikari severity scale

Supplement 154 Number of GE episodes and RV GE episodes reported from Dose 1 up to before Dose 2, by severity using the 24-point Clark scale - Total vaccinated cohort

Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	**Mild (1-8)**	164	86.3	69	73.4
	Moderate (9-16)	26	13.7	21	22.3
	Severe (≥17)	0	0.0	0	0.0
	Unknown	0	0.0	4	4.3
	Any	190	100	94	100
RV GE	**Mild (1-8)**	0	0.0	0	0.0
	Moderate (9-16)	1	100	5	100
	Severe (≥17)	0	0.0	0	0.0
	Any	1	100	5	100

n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported

Any = any specified symptom reported, regardless of Vesikari severity scale

Supplement 155 Percentage of subjects with RV GE episodes reported from Dose 1 up to before Dose 2, by G serotype and P genotype - Total vaccinated cohort

Serotype	HRV N= 2646		Placebo 1348	
	n	%	n	%
Any	1	0.0	5	0.4
G3	1	0.0	2	0.1
G9	0	0.0	3	0.2
P8 wild type	1	0.0	5	0.4

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 156 Number of RV GE episodes reported from Dose 1 up to before Dose 2, by G serotype and P genotype - Total vaccinated cohort

Country	Serotype	HRV N'= 1 n	%	Placebo N'= 5 N	%
Spain	**G9 and P8wt**	0	0.0	3	60.0
	G3 and P8wt	1	100	2	40.0
All countries	**G9 and P8wt**	0	0.0	3	60.0
	G3 and P8wt	1	100	2	40.0

N' = number of RV GE episodes reported
n/% = number/percentage of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type

Supplement 157 Duration (in years) of the follow-up period from Dose 1 up to before Dose 2 - Total vaccinated cohort

Duration (years) of follow-up period	HRV N= 2646	Placebo N= 1348
Total	418.9	213.1
Mean	0.158	0.158
SD	0.044	0.044
Minimum	0.025	0.074
Q1	0.140	0.140
Median	0.167	0.164
Q3	0.178	0.178
Maximum	0.745	0.882

N = number of subjects included in each group
Total = sum of follow-up period expressed in year
SD = standard deviation
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 158 Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from Dose 1 up to before Dose 2 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	1	0.0	0.0	0.2	89.8	8.9	99.8	0.019
Placebo	1348	5	0.4	0.1	0.9				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 159 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and efficacy of the vaccine from Dose 1 up to before Dose 2 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	0	0.0	0.0	0.1	100	-23.3	100	0.038
Placebo	1348	3	0.2	0.0	0.6				

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 160 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and efficacy of the vaccine from Dose 1 up to before Dose 2 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	0	0.0	0.0	0.1	-	-	-	-
Placebo	1348	0	0.0	0.0	0.3				

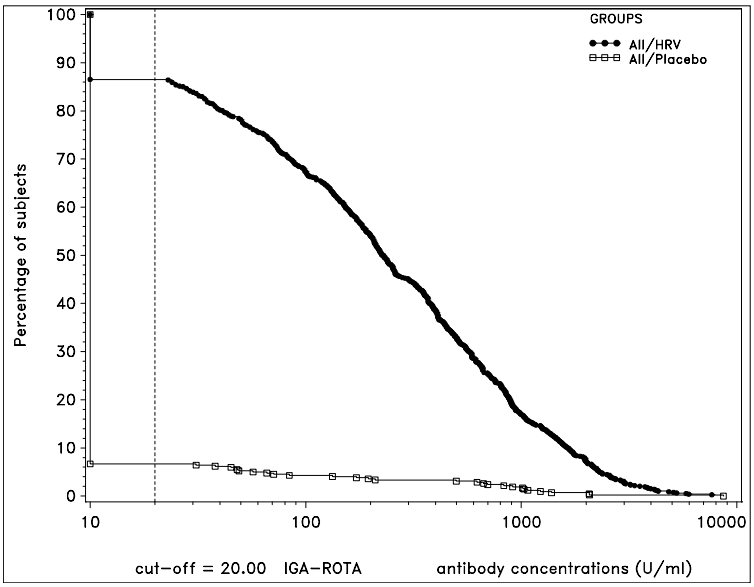
N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 161 Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 – pooled countries – ATP cohort for immunogenicity



Supplement 162 Difference in percentage of subjects who seroconverted for anti-rotavirus IgA antibody one to two months after Dose 2 of HRV vaccine or placebo (Visit 3) between HRV and placebo groups – pooled countries - ATP cohort for immunogenicity

						Difference in seroconversion rate			
								95 % CI	
Group	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
HRV	787	86.5	Placebo	420	6.7	HRV - Placebo	79.86	76.19	82.96

N = number of subjects with available results

% = percentage of subjects who seroconverted one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 163 Seroconversion rates and GMCs for anti-rotavirus IgA antibodies, by feeding criteria – pooled countries - ATP cohort for immunogenicity

				≥ 20 U/ML				GMC		
						95% CI			95% CI	
Breast feeding	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
For at least one dose	**HRV**	**PRE**	577	0	0.0	0.0	0.6	< 20	-	-
		PII(M3-M4)	574	491	85.5	82.4	88.3	185.8	161.4	213.9
		PII(M5)	127	104	81.9	74.1	88.2	113.4	86.6	148.3
	Placebo	**PRE**	321	0	0.0	0.0	1.1	< 20	-	-
		PII(M3-M4)	321	17	5.3	3.1	8.3	< 20	-	-
		PII(M5)	64	6	9.4	3.5	19.3	< 20	-	-
At none of the doses	**HRV**	**PRE**	217	0	0.0	0.0	1.7	< 20	-	-
		PII(M3-M4)	213	190	89.2	84.2	93.0	231.5	185.9	288.2
		PII(M5)	57	48	84.2	72.1	92.5	113.3	75.6	169.9
	Placebo	**PRE**	101	0	0.0	0.0	3.6	< 20	-	-
		PII(M3-M4)	99	11	11.1	5.7	19.0	< 20	-	-
		PII(M5)	26	8	30.8	14.3	51.8	22.2	12.6	39.4

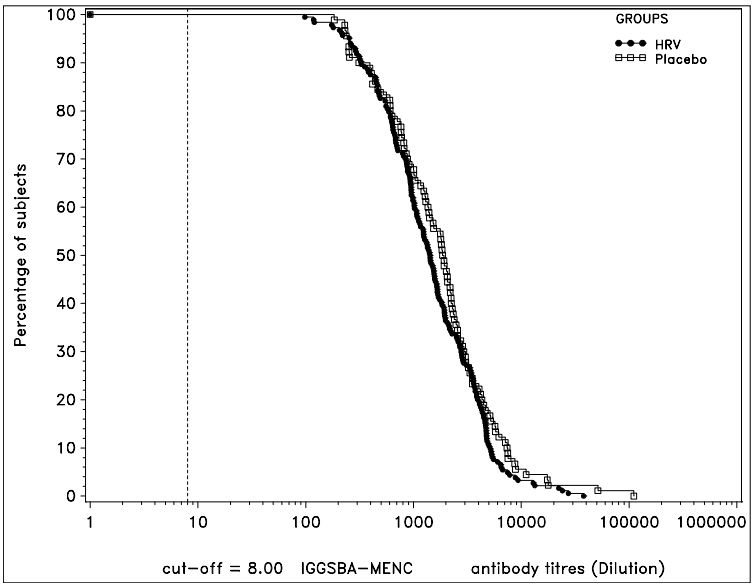
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Supplement 164 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at Visit 3 (4), by feeding criteria – pooled countries – ATP cohort for immunogenicity

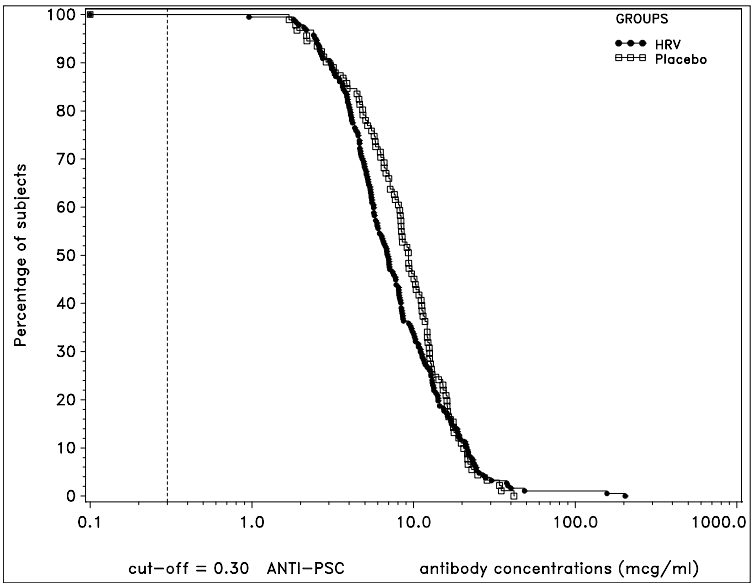
				GMC		
					95% CI	
Breast feeding	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
For at least one dose	**HRV**	**PII(M3-M4)**	491	304.5	270.7	342.5
		PII(M5)	104	193.9	156.0	241.1
	Placebo	**PII(M3-M4)**	17	325.2	150.5	702.8
		PII(M5)	6	241.9	67.1	872.6
At none of the doses	**HRV**	**PII(M3-M4)**	190	338.6	282.5	406.0
		PII(M5)	48	178.6	126.1	253.1
	Placebo	**PII(M3-M4)**	11	244.8	78.5	763.4
		PII(M5)	8	134.4	43.8	411.9

N = number of subjects who seroconverted for anti-rotavirus IgA antibodies
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

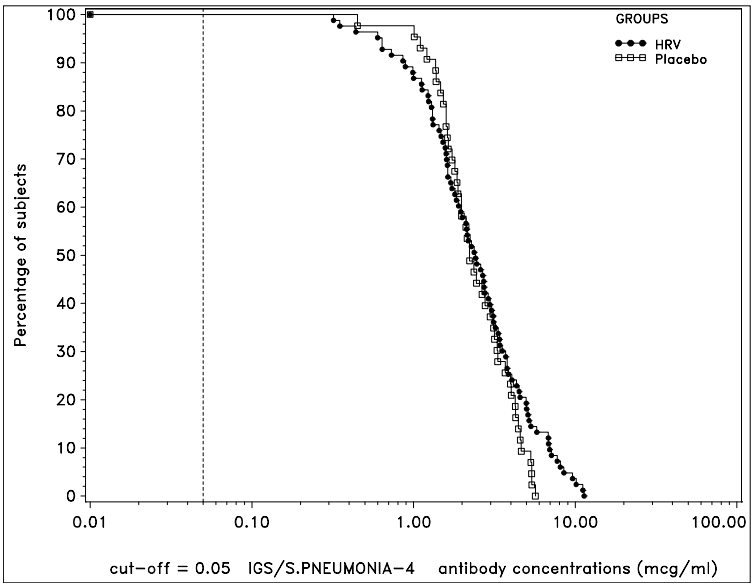
Supplement 165 Reverse cumulative curves for SBA-MenC antibody concentrations post Dose 3 of Meningitec – Spain – ATP cohort for immunogenicity



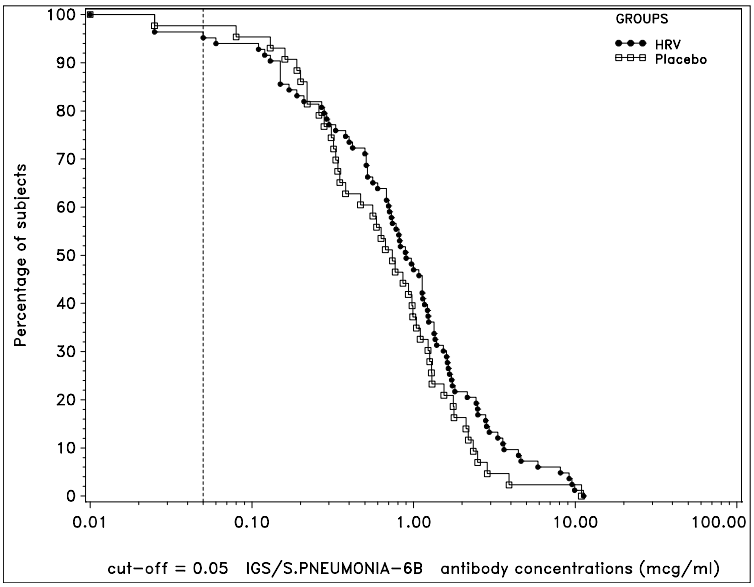
Supplement 166 Reverse cumulative curves for anti-PSC antibody concentrations post Dose 3 of Meningitec – Spain – ATP cohort for immunogenicity



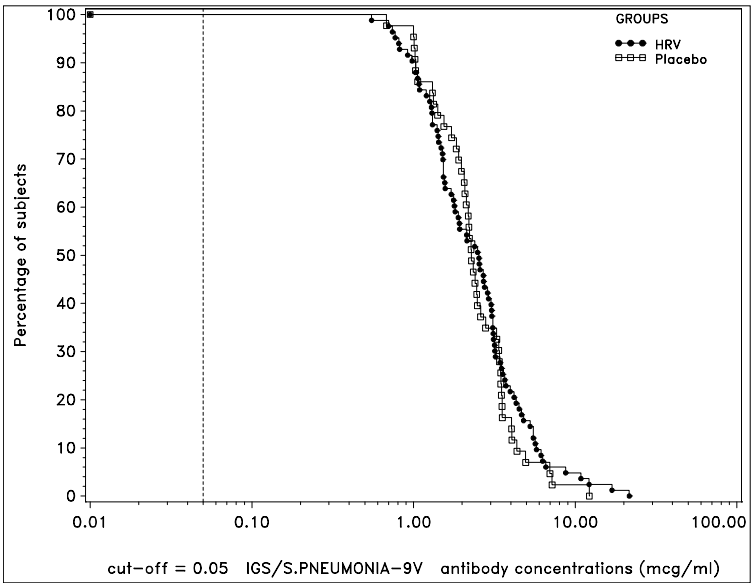
Supplement 167 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 4 antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



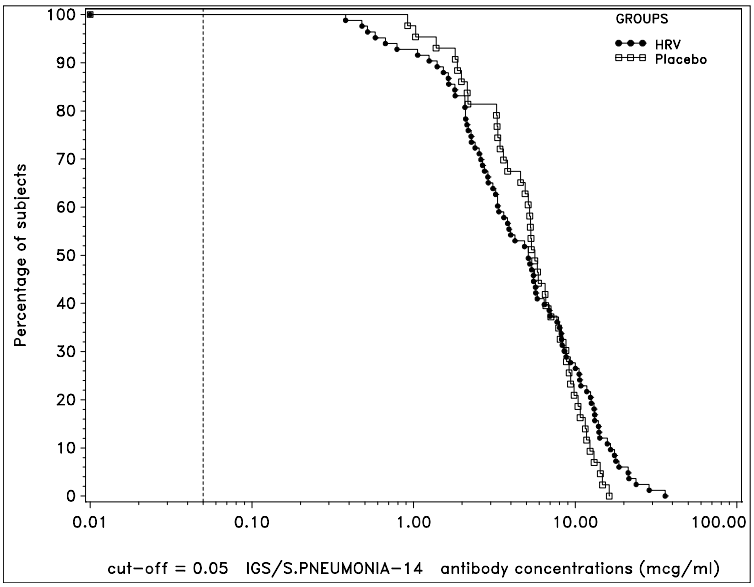
Supplement 168 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 6B antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



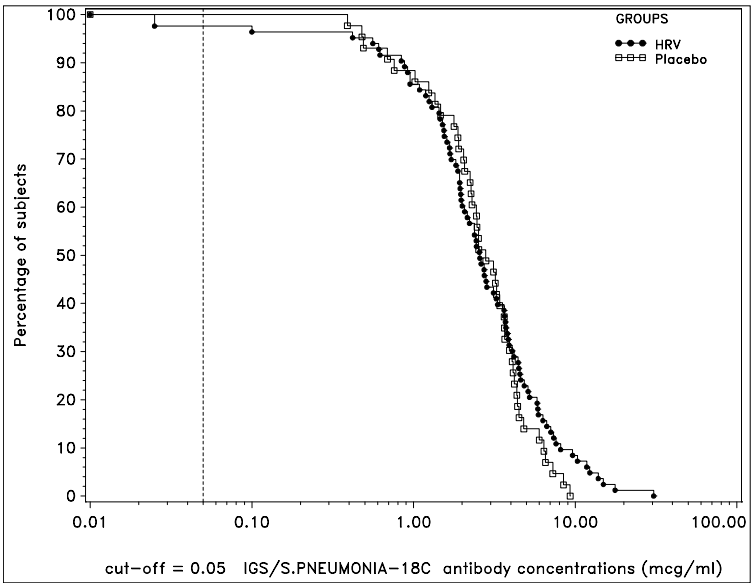
Supplement 169 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 9V antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



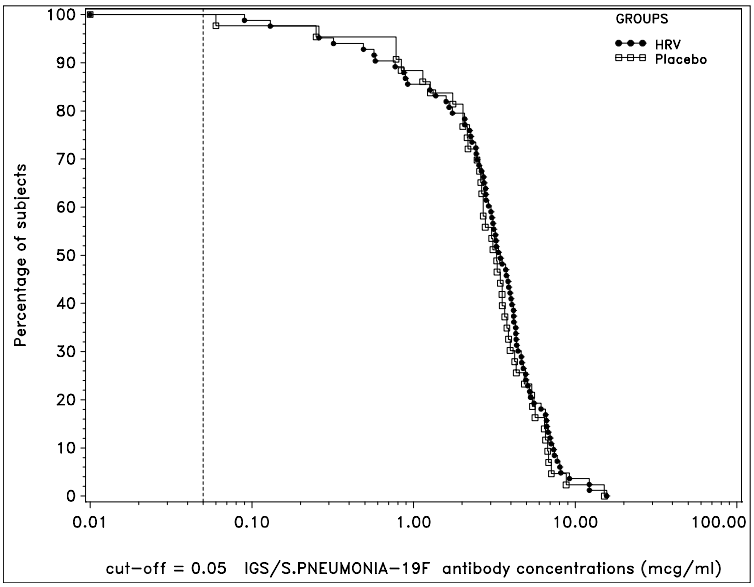
Supplement 170 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 14 antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



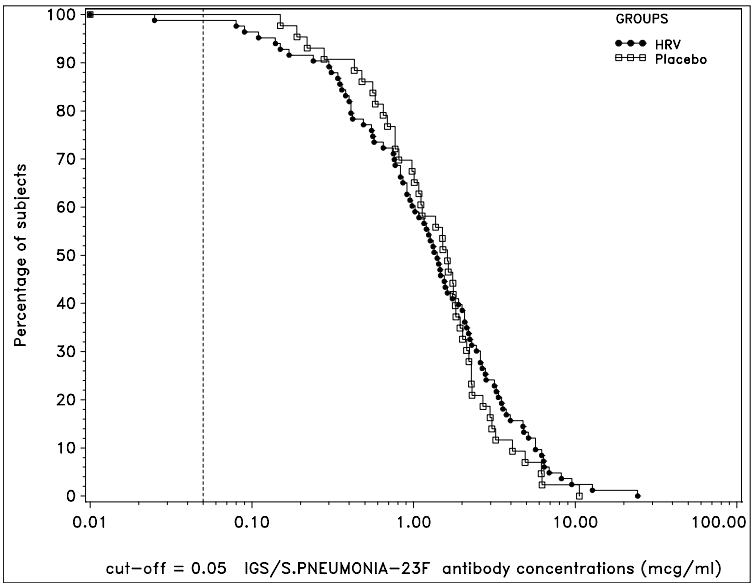
Supplement 171 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 18C antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



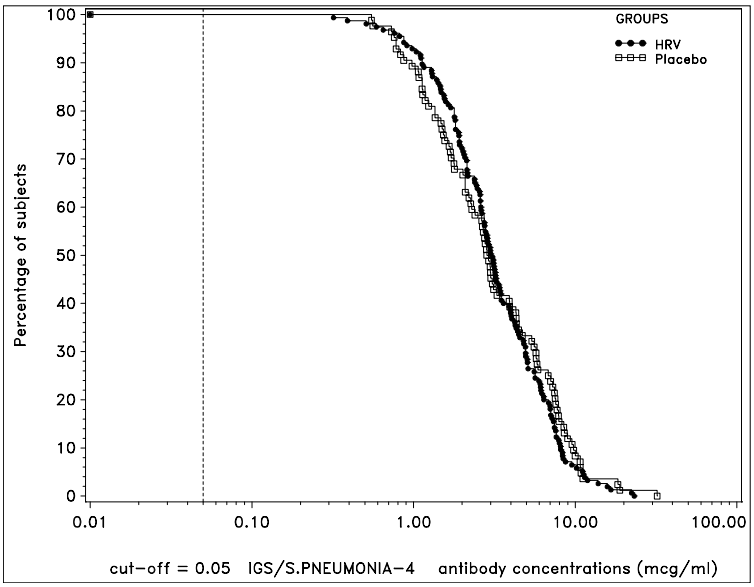
Supplement 172 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 19F antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



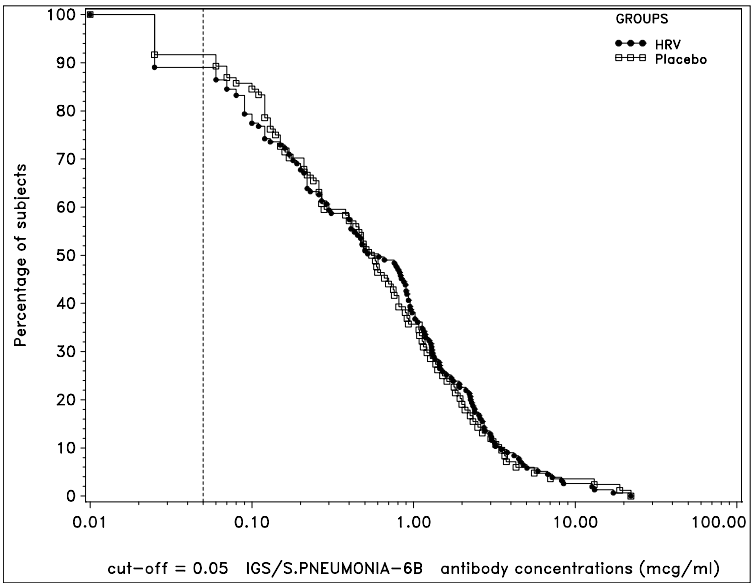
Supplement 173 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 23F antibody concentrations post Dose 3 of Prevenar – France – ATP cohort for immunogenicity



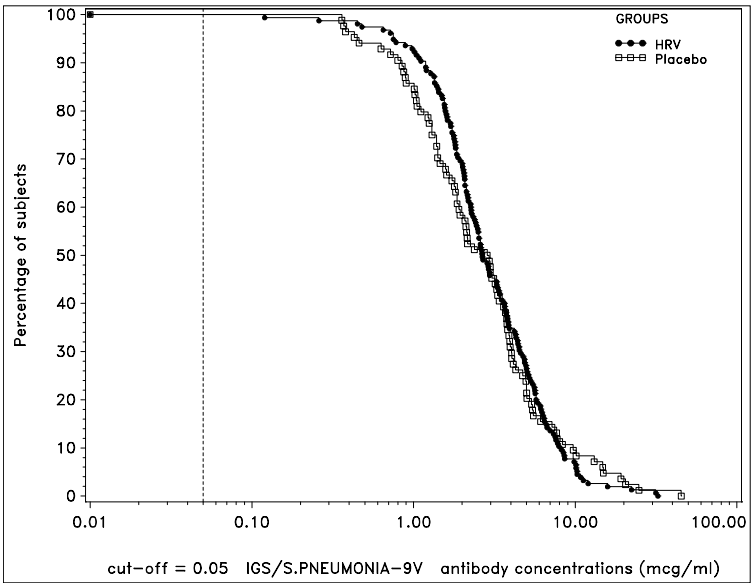
Supplement 174 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 4 antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



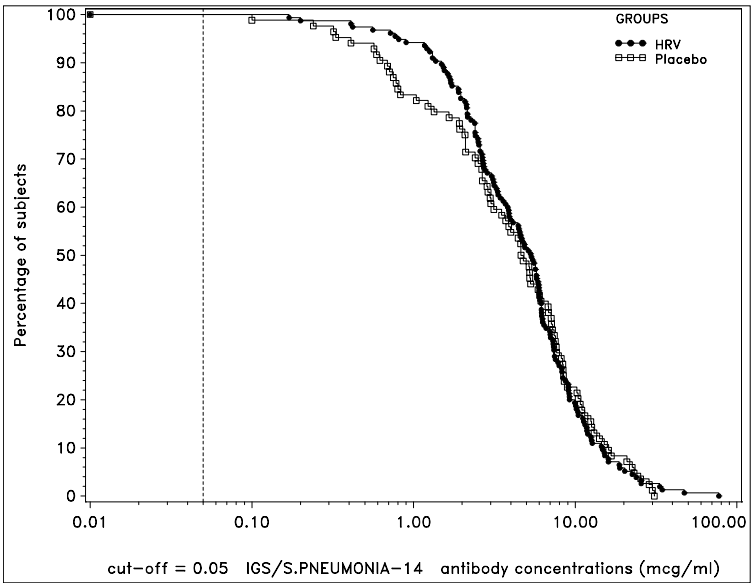
Supplement 175 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 6B antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



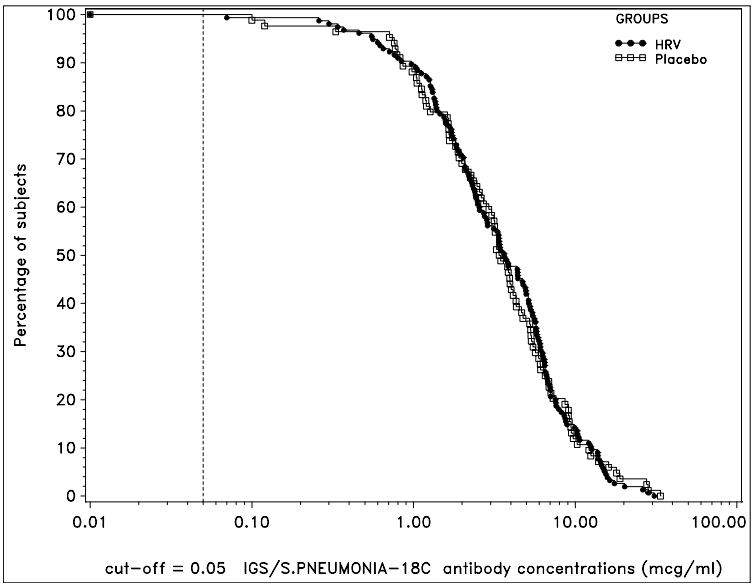
Supplement 176 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 9V antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



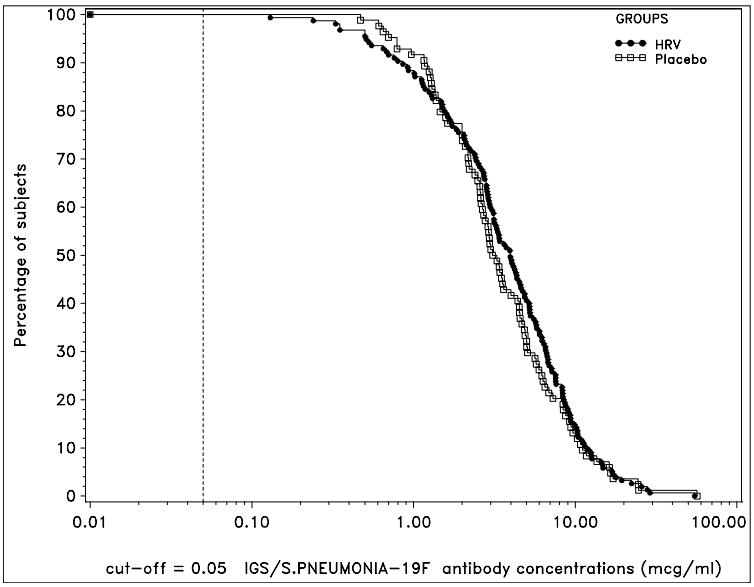
Supplement 177 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 14 antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



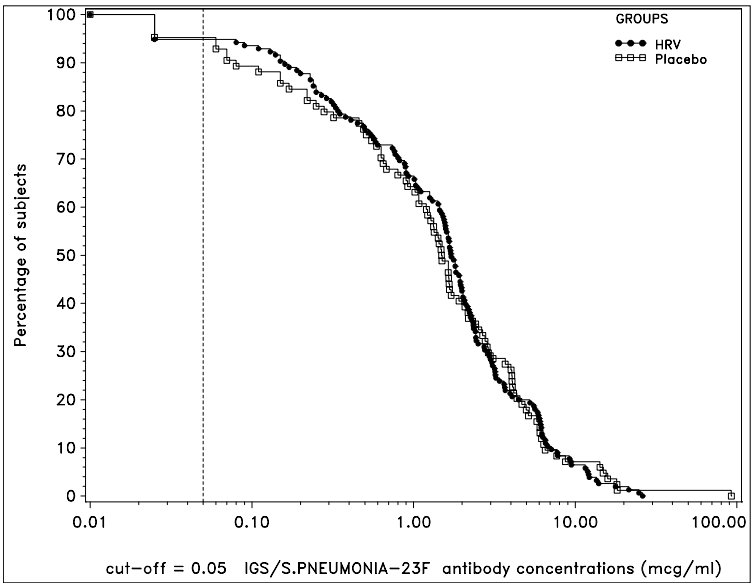
Supplement 178 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 18C antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



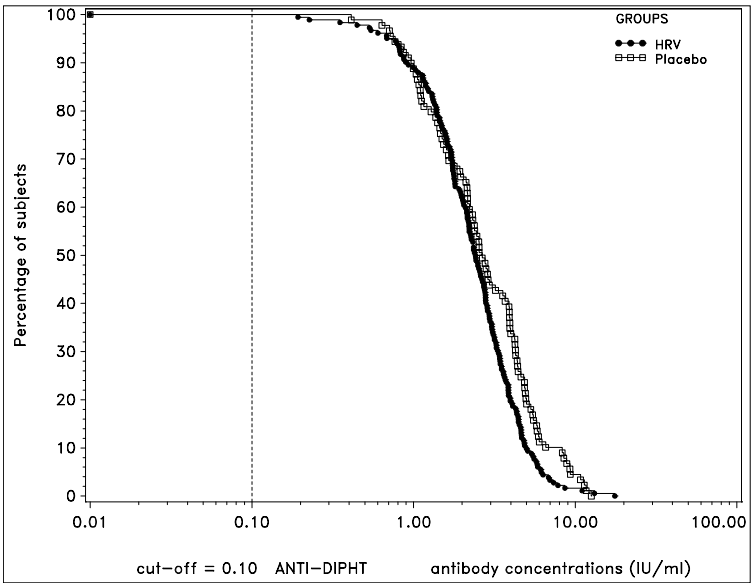
Supplement 179 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 19F antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



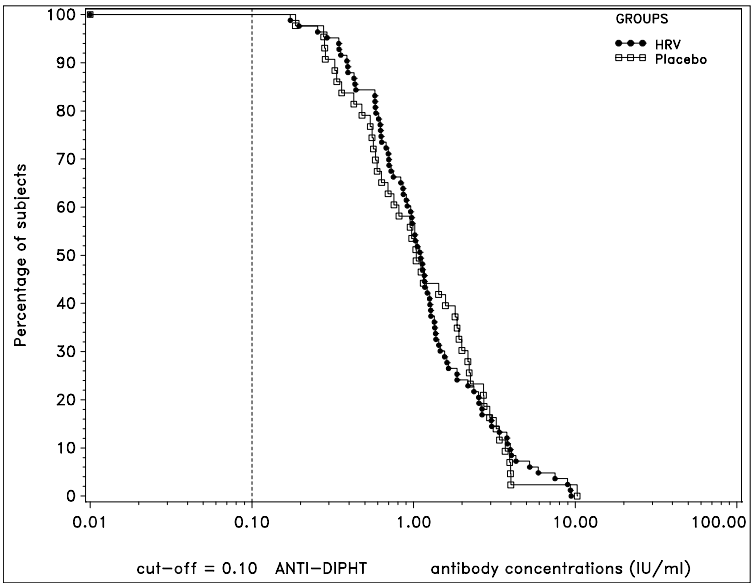
Supplement 180 Reverse cumulative curves for *Streptococcus pneumoniae* serotype 23F antibody concentrations post Dose 3 of Prevenar – Germany – ATP cohort for immunogenicity



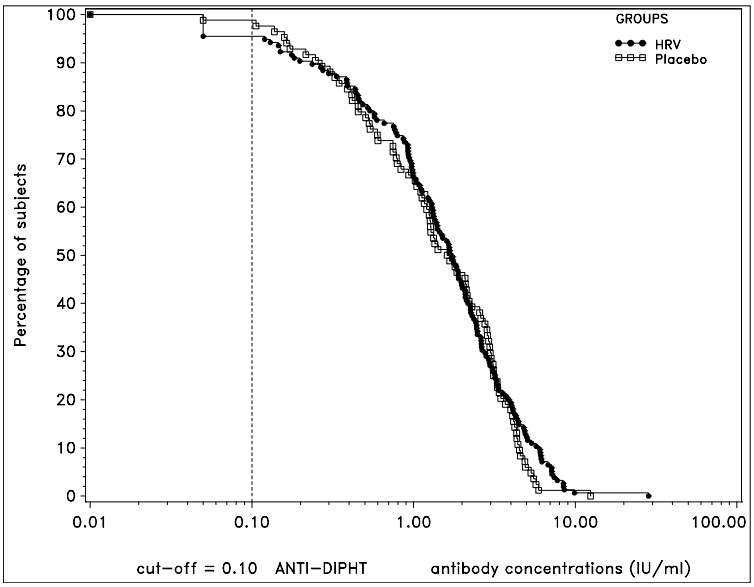
Supplement 181 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



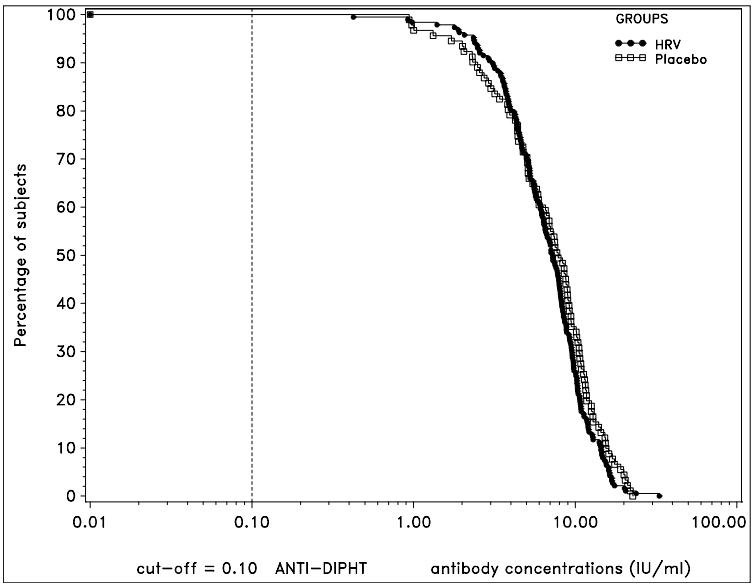
Supplement 182 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



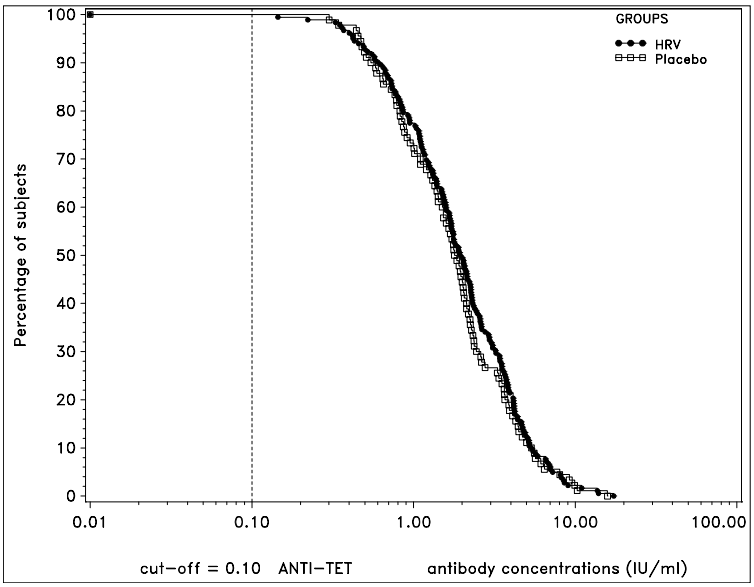
Supplement 183 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



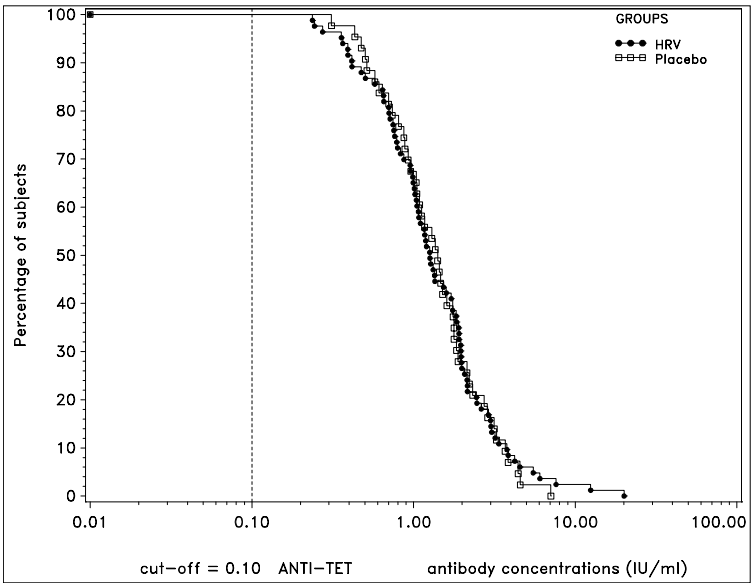
Supplement 184 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



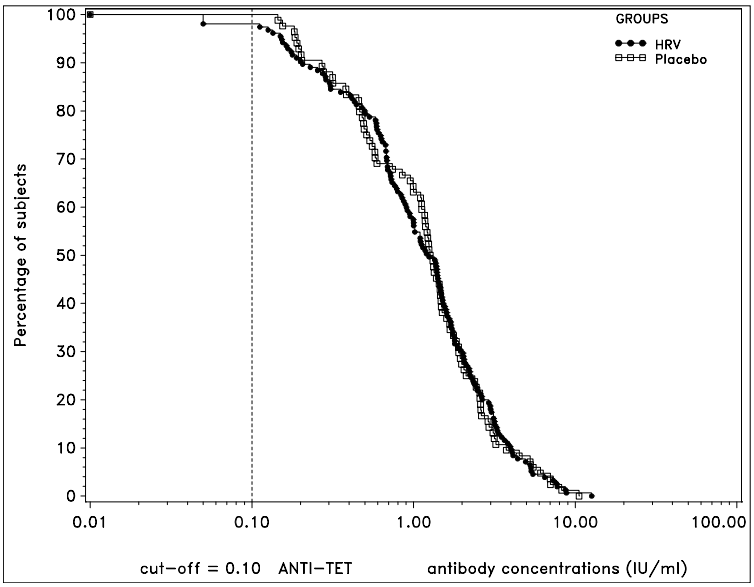
Supplement 185 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



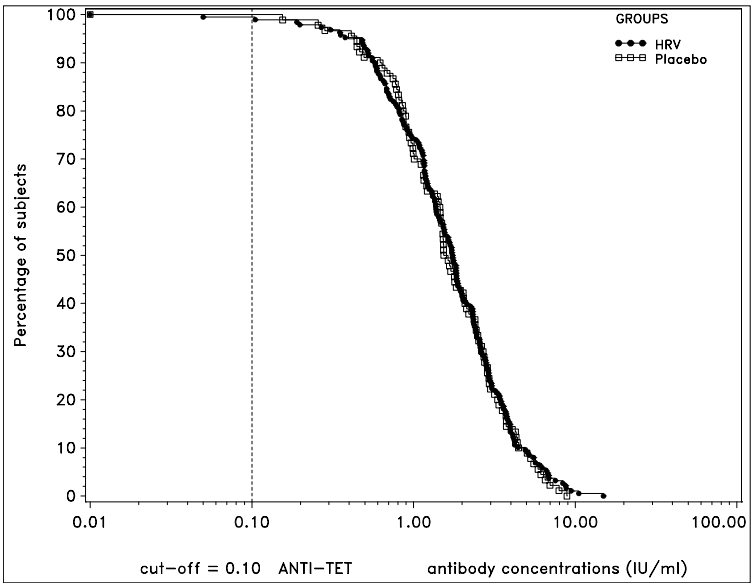
Supplement 186 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



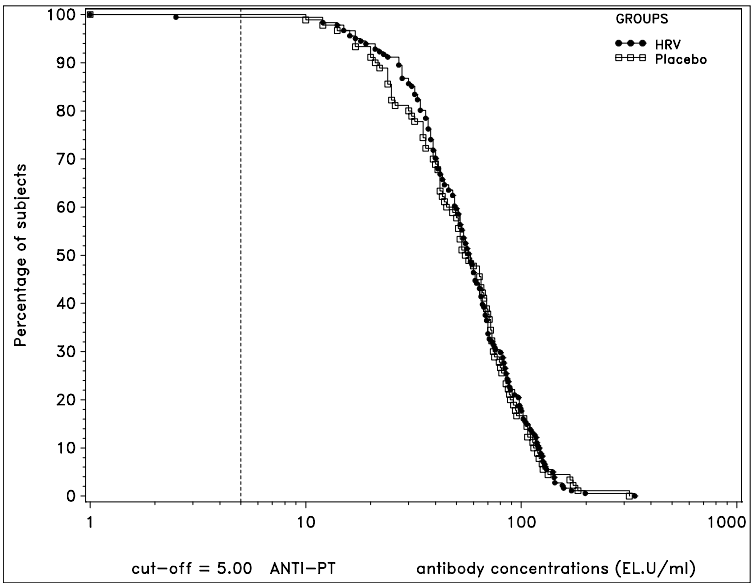
Supplement 187 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



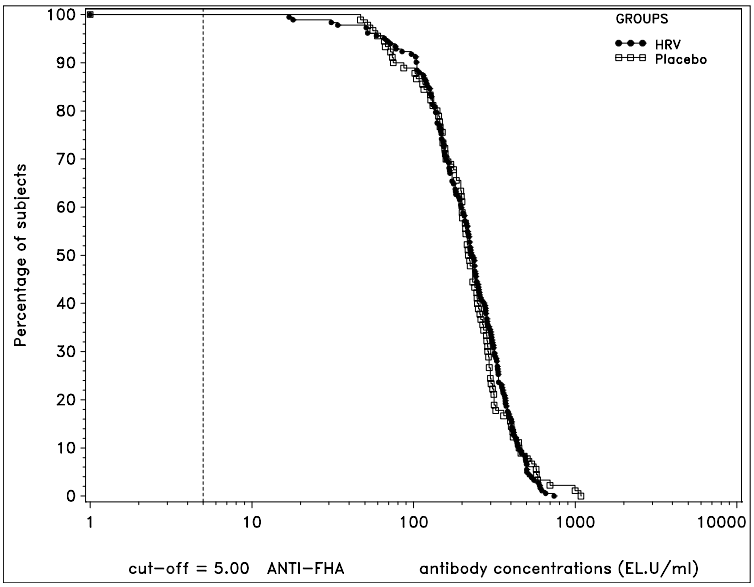
Supplement 188 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



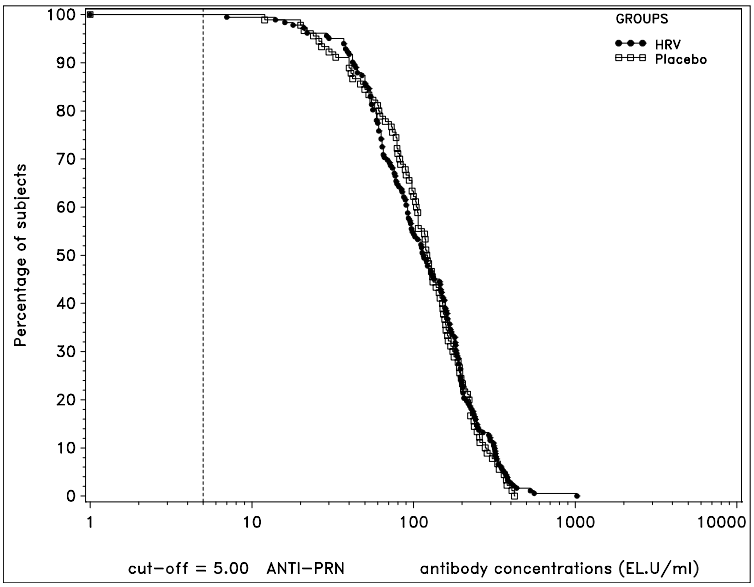
Supplement 189 Reverse cumulative curves for anti-PT antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



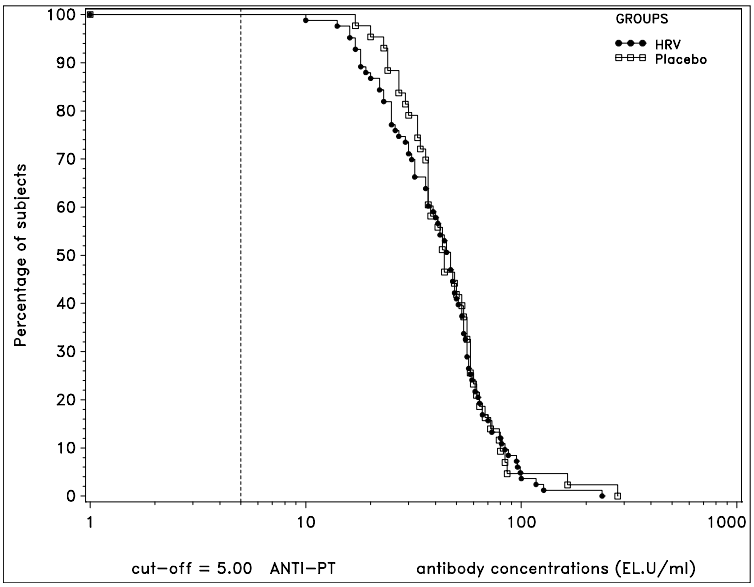
Supplement 190 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



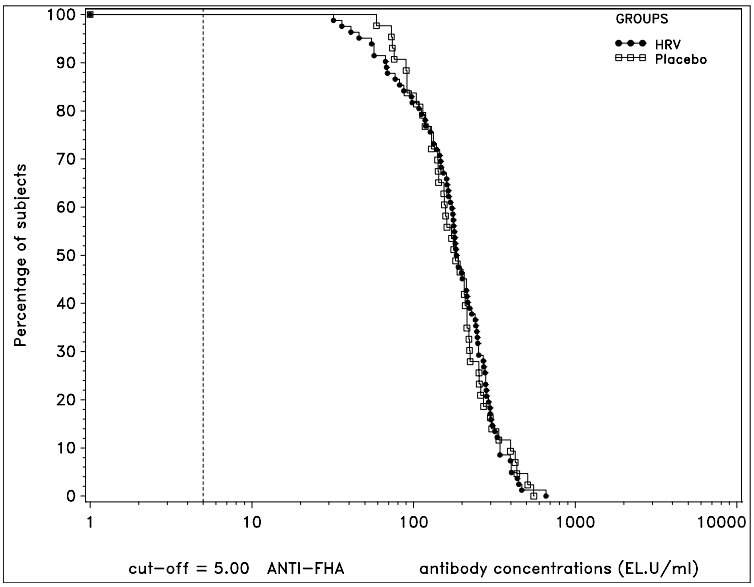
Supplement 191 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



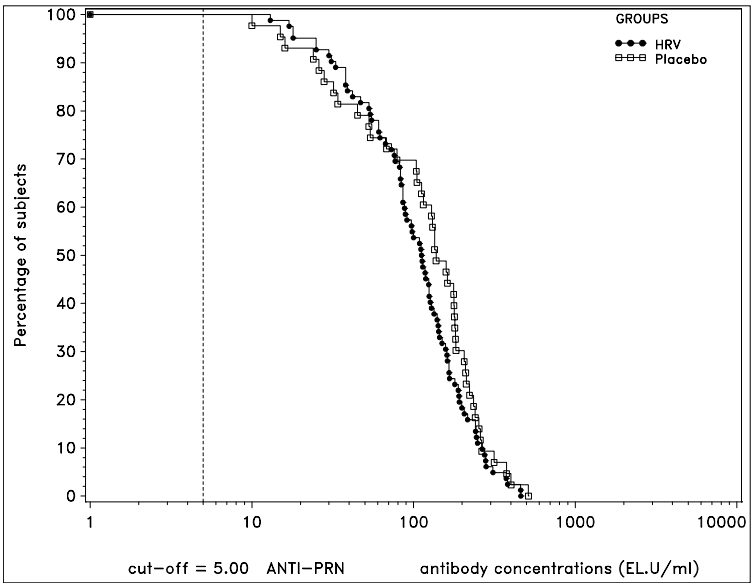
Supplement 192 Reverse cumulative curves for anti-PT antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



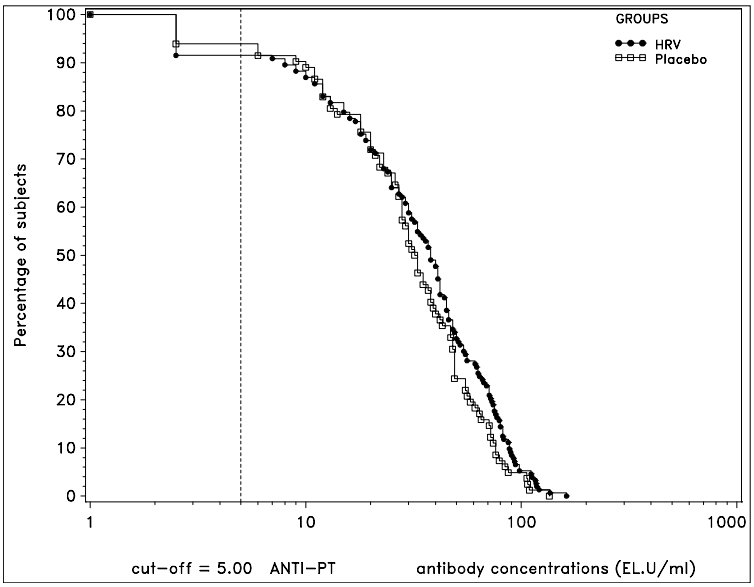
Supplement 193 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



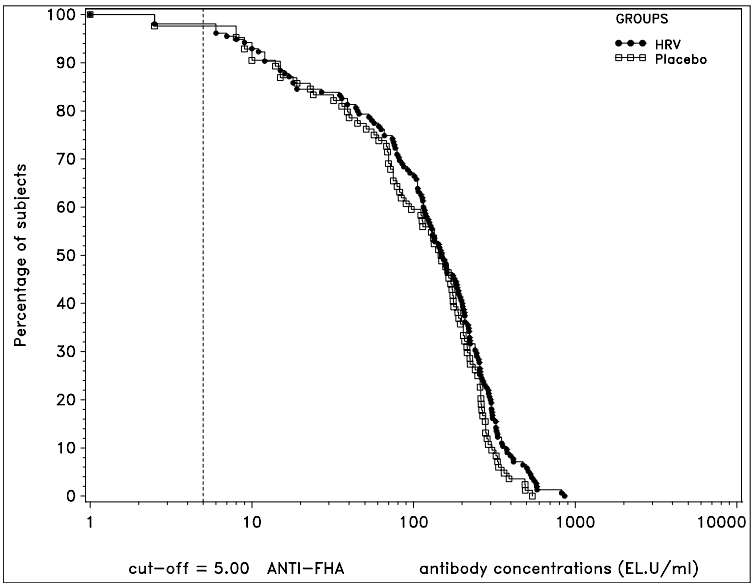
Supplement 194 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



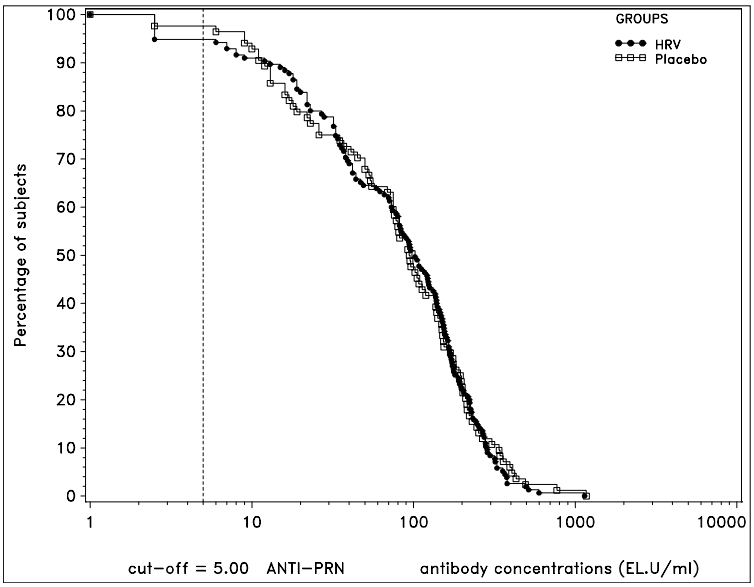
Supplement 195 Reverse cumulative curves for anti-PT antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



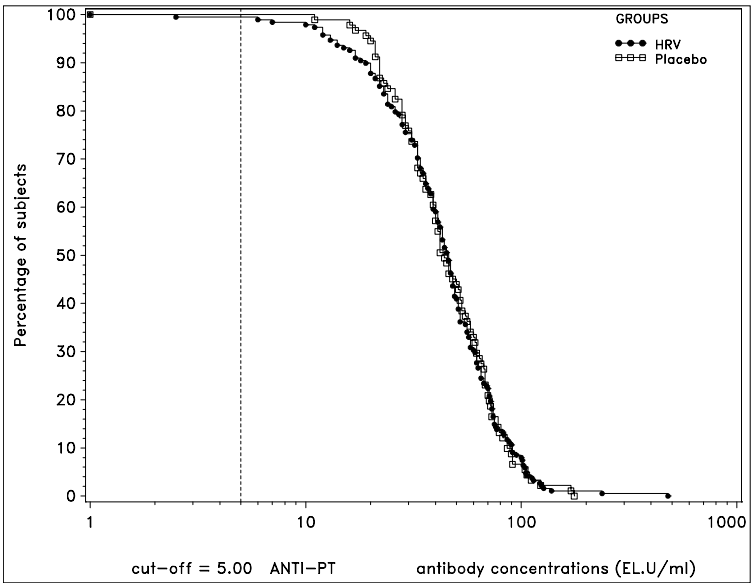
Supplement 196 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



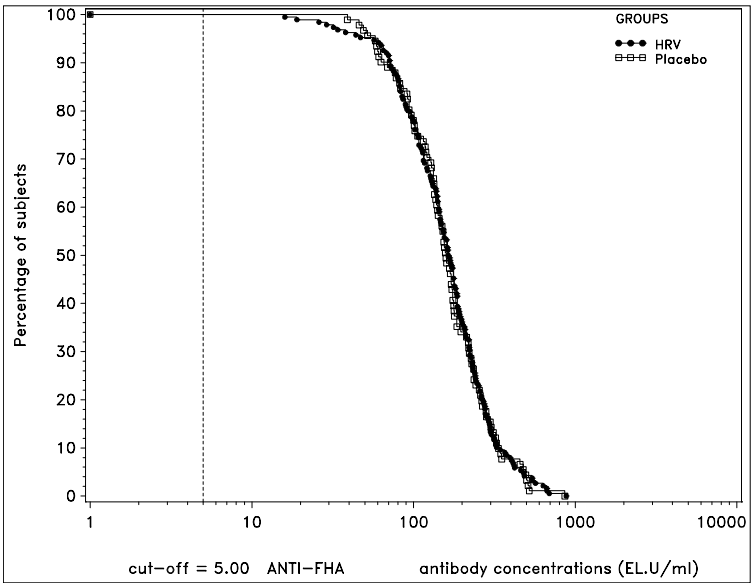
Supplement 197 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



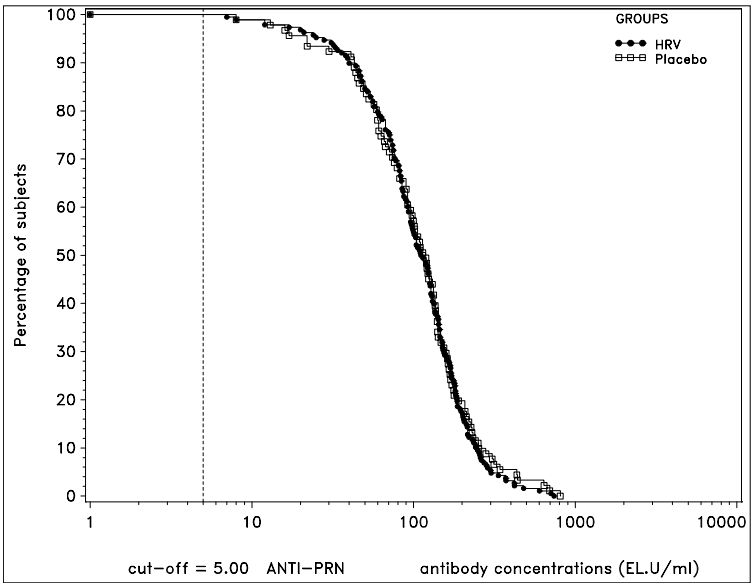
Supplement 198 Reverse cumulative curves for anti-PT antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



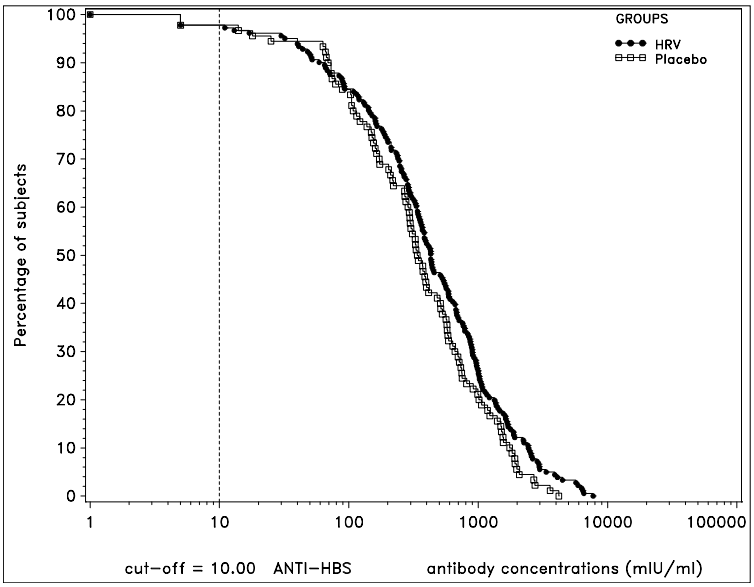
Supplement 199 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



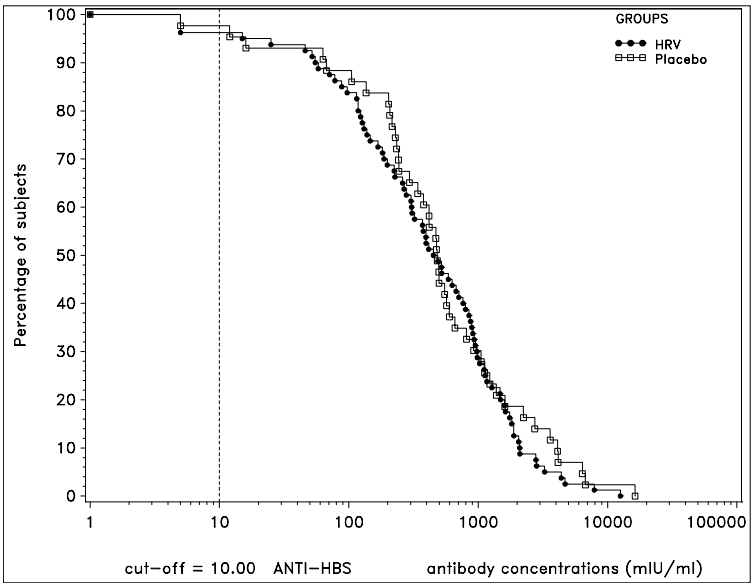
Supplement 200 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



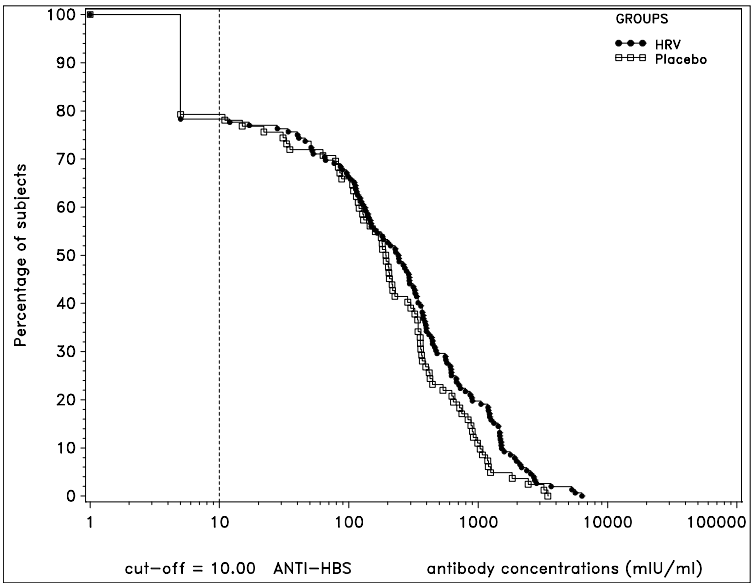
Supplement 201 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



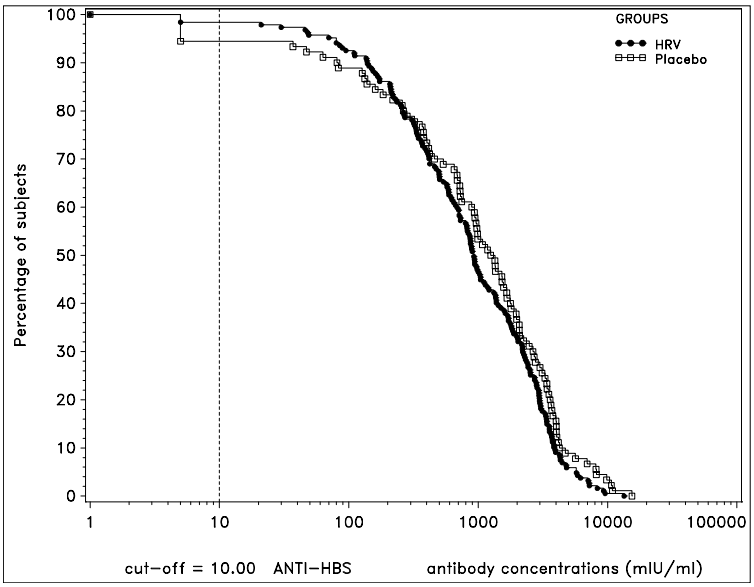
Supplement 202 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



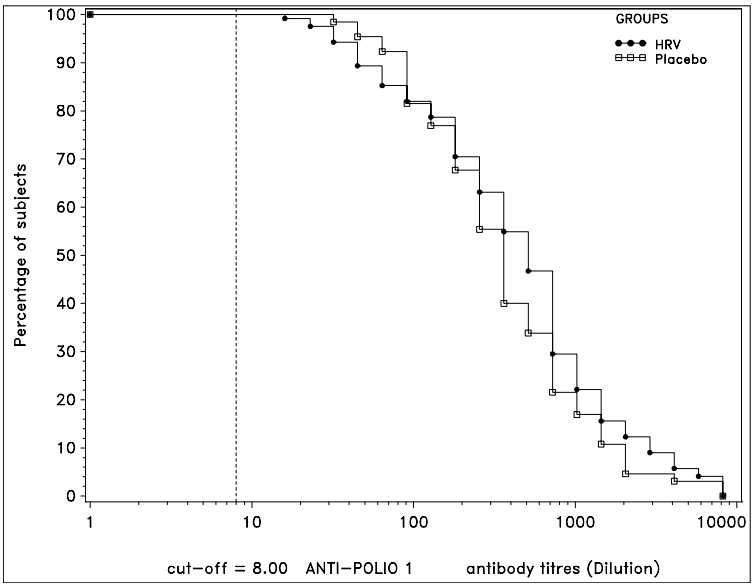
Supplement 203 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



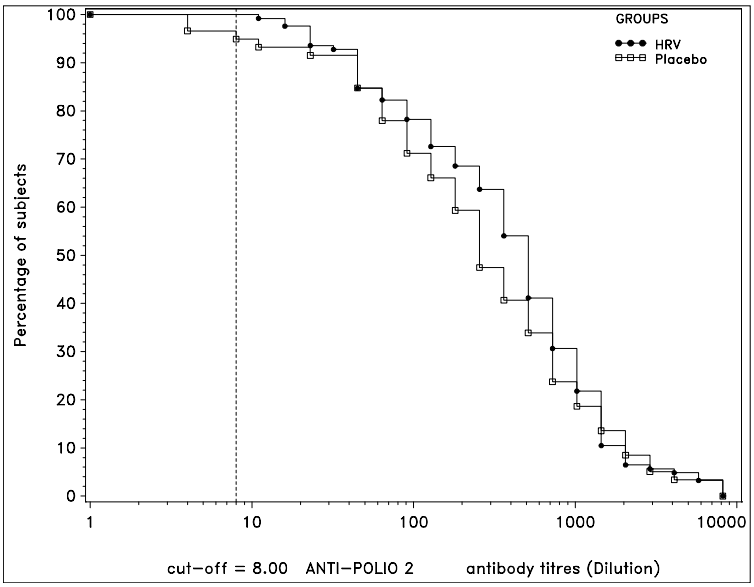
Supplement 204 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



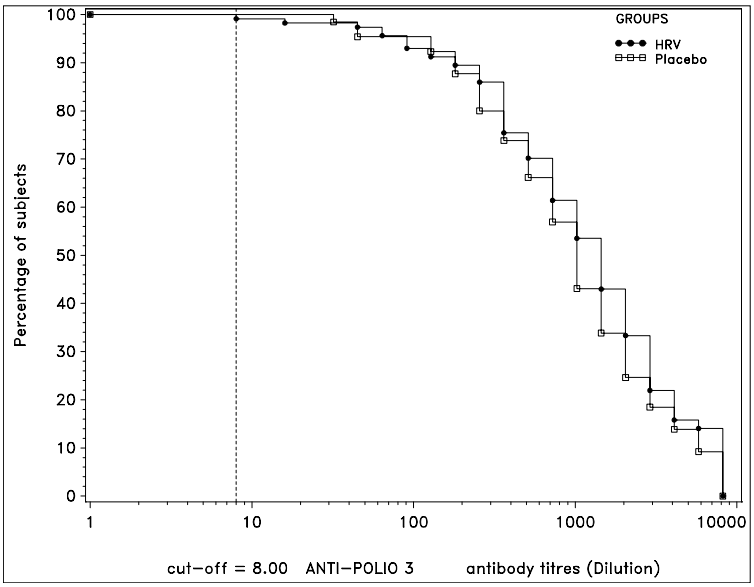
Supplement 205 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



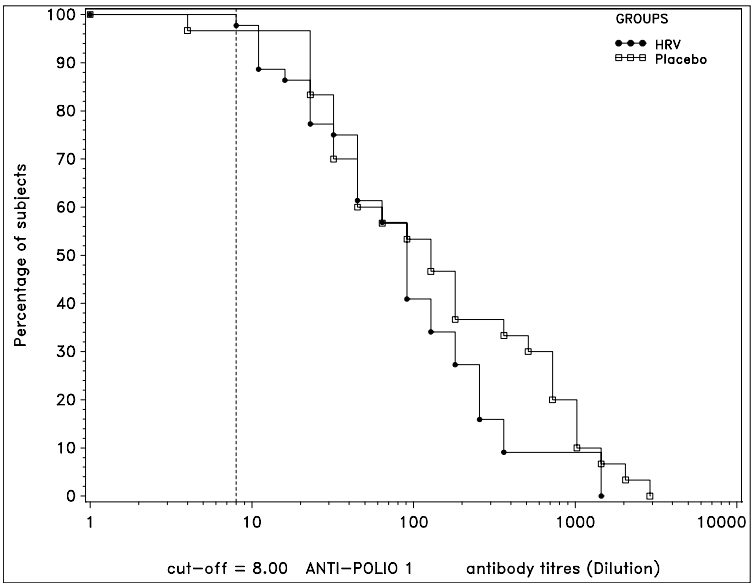
Supplement 206 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



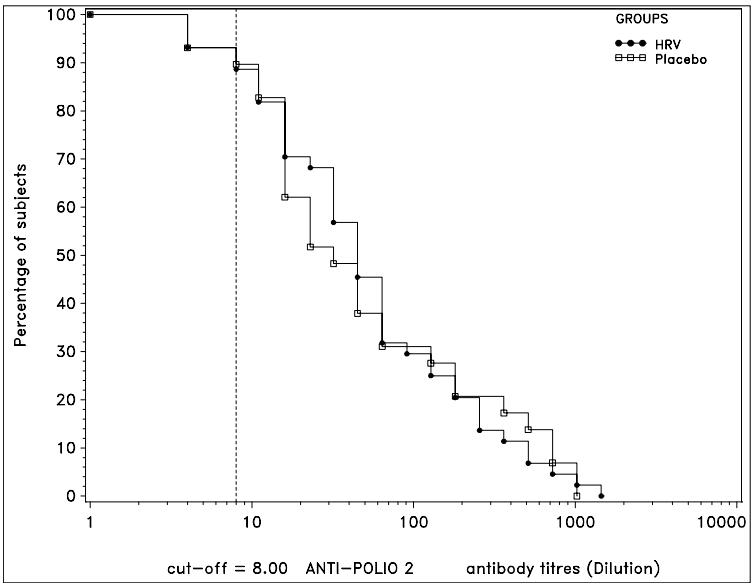
Supplement 207 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



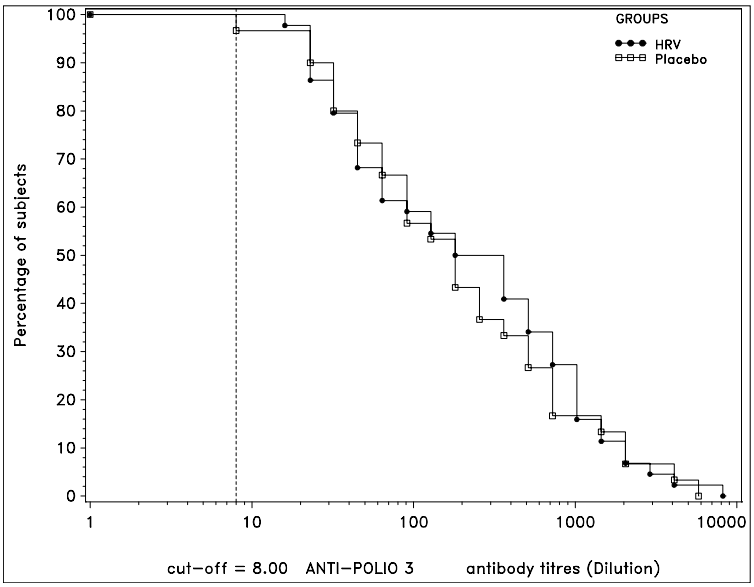
Supplement 208 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



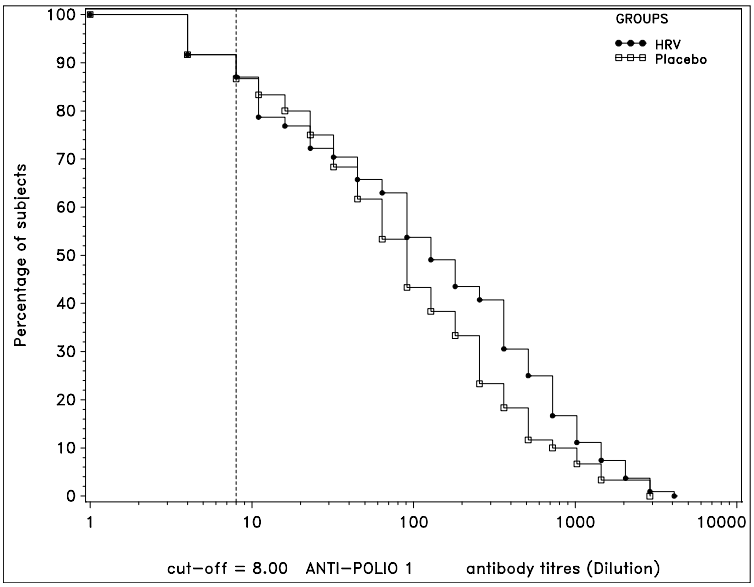
Supplement 209 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



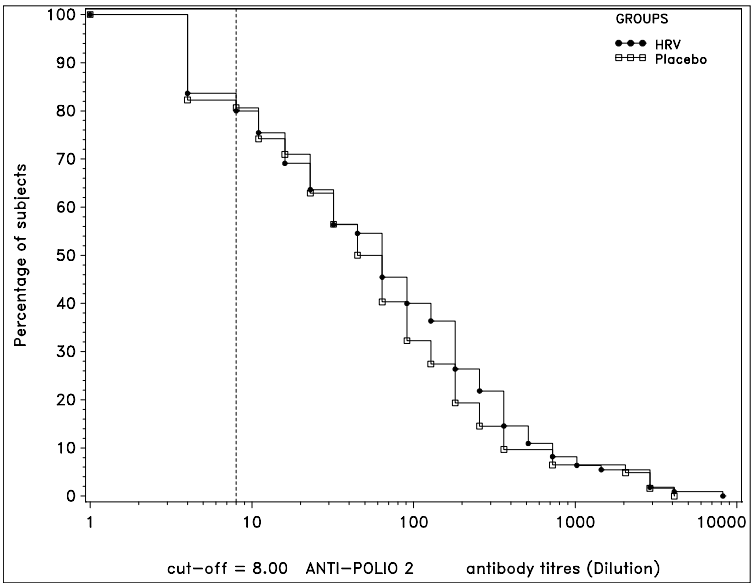
Supplement 210 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



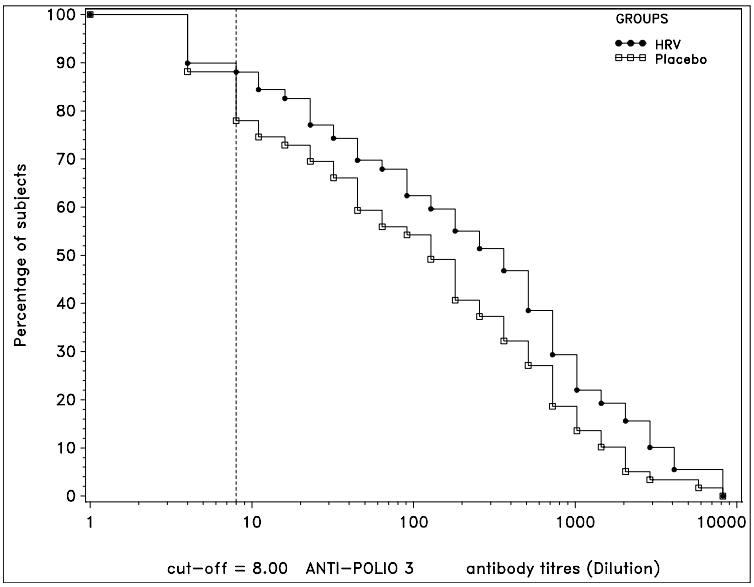
Supplement 211 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



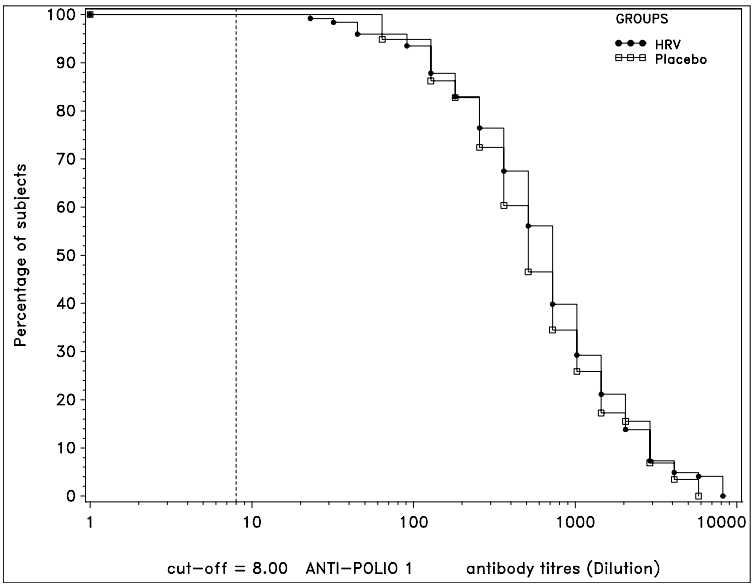
Supplement 212 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



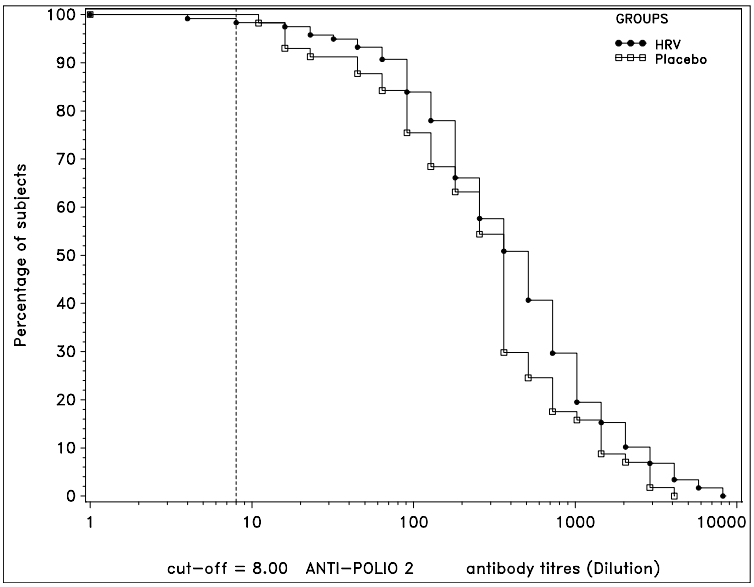
Supplement 213 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



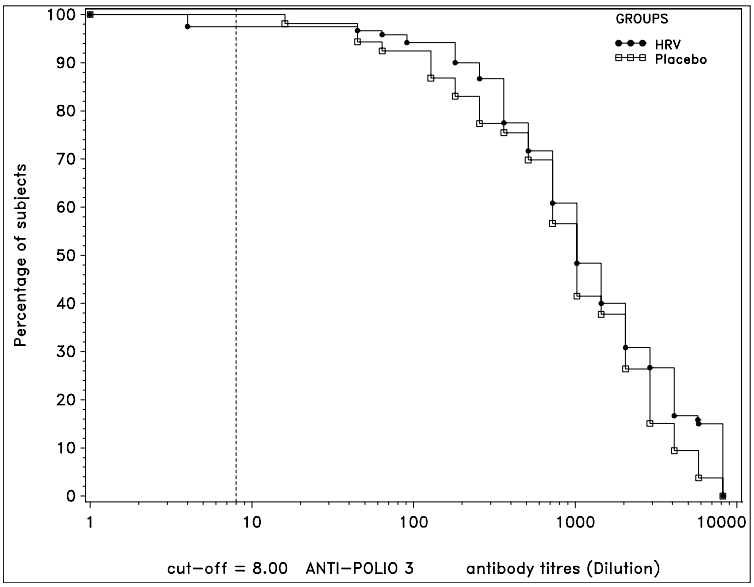
Supplement 214 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



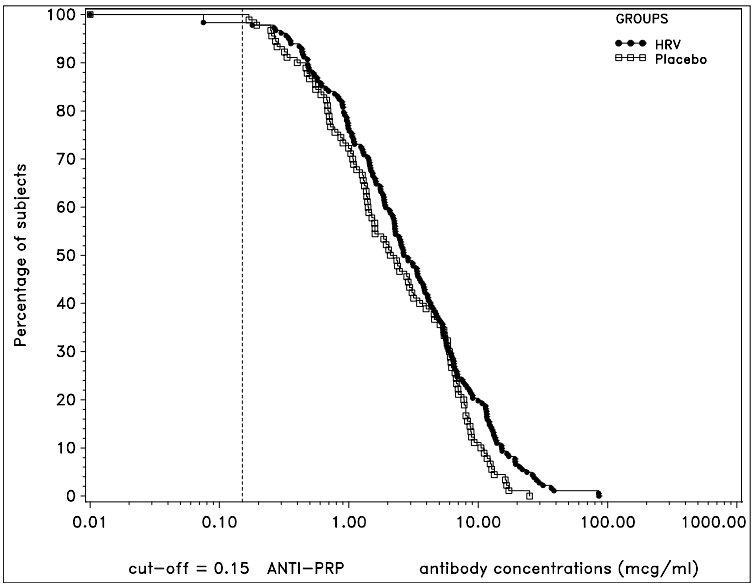
Supplement 215 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



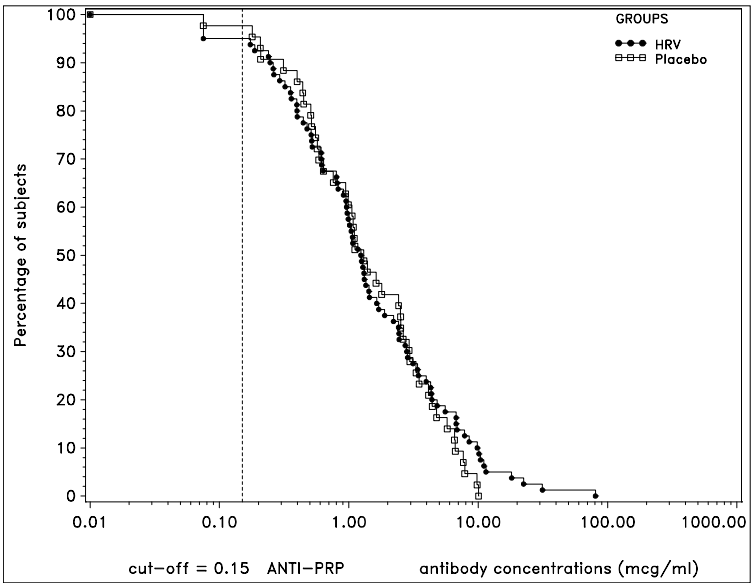
Supplement 216 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



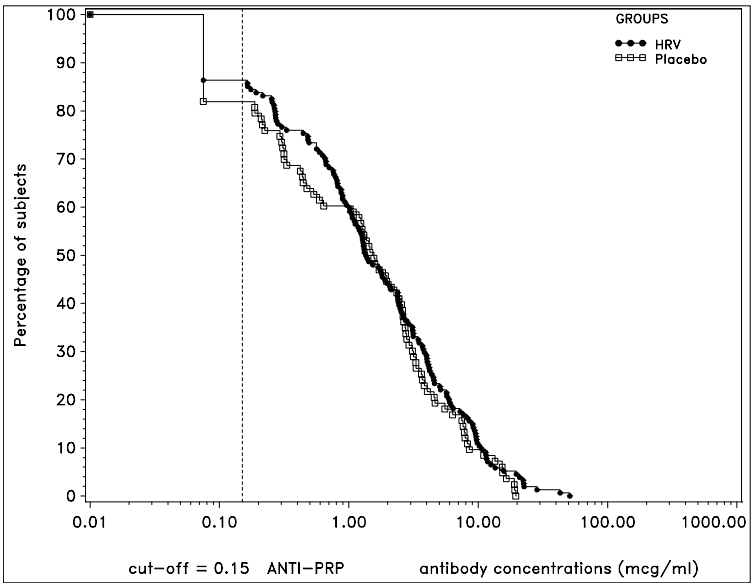
Supplement 217 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 3 of childhood vaccinations – Czech Republic – ATP cohort for immunogenicity



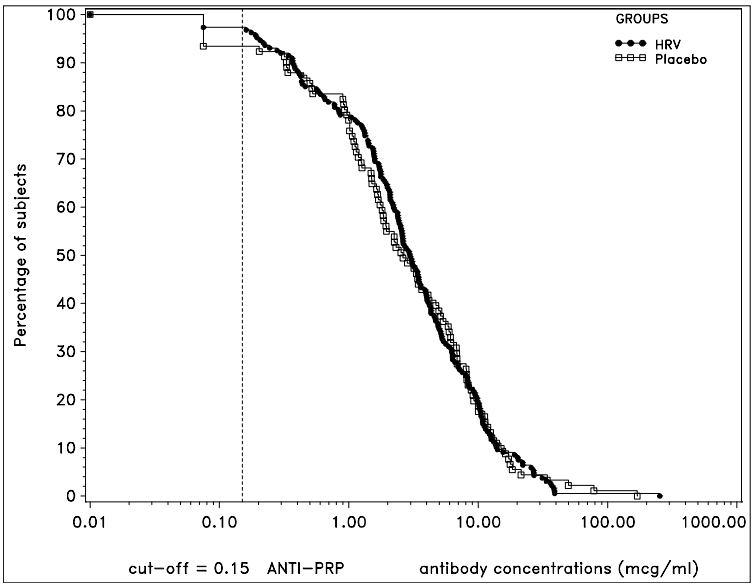
Supplement 218 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 3 of childhood vaccinations – France – ATP cohort for immunogenicity



Supplement 219 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 3 of childhood vaccinations – Germany – ATP cohort for immunogenicity



Supplement 220 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 3 of childhood vaccinations – Spain – ATP cohort for immunogenicity



Supplement 221 Difference in seropositivity rates post Dose 3 of Meningitec between placebo and HRV groups, for anti-SBA-MENC titer ≥8 - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	90	100	HRV	184	100	Placebo - HRV	0.00	-4.09	2.05

N = number of subjects with available results

% = percentage of subjects with IGGSBA-MENC titer ≥ 8 1/DIL.

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 222 Difference in seropositivity rates post Dose 3 of Meningitec between placebo and HRV groups, for SBA-MENC titer ≥128- ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	90	100	HRV	184	98.4	Placebo - HRV	1.63	-2.49	4.68

N = number of subjects with available results

% = percentage of subjects with IGGSBA-MENC titer ≥ 128 1/DIL.

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 223 Difference in seropositivity rates post Dose 3 of Meningitec between placebo and HRV groups, for Anti-PSC concentration ≥ 0.3 mcg/ml - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	91	100	HRV	187	100	Placebo - HRV	0.00	-4.05	2.01

N = number of subjects with available results

% = percentage of subjects with anti-PSC concentration ≥ 0.3 μg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 224 Difference in seropositivity rates post Dose 3 of Meningitec between placebo and HRV groups, for Anti-PSC concentration ≥ 2 mcg/ml - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	91	96.7	HRV	187	97.9	Placebo - HRV	-1.16	-7.27	2.73

N = number of subjects with available results

% = percentage of subjects with anti-PSC concentration ≥ 2 μg/ml.

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 225 Difference in seropositivity rates post Dose 3 of Prevenar between placebo and HRV groups, for *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F antibody concentration ≥ 0.05 mcg/ml - ATP cohort for immunogenicity

								Difference in seropositivity rate			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
PNEUMONIA-4	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	100	HRV	155	100	Placebo - HRV	0.00	-4.37	2.42
PNEUMONIA-6B	**France**	Placebo	43	97.7	HRV	83	96.4	Placebo - HRV	1.29	-8.72	8.20
	Germany	Placebo	84	91.7	HRV	155	89.0	Placebo - HRV	2.63	-6.18	10.04
PNEUMONIA-9V	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	100	HRV	155	100	Placebo - HRV	0.00	-4.37	2.42
PNEUMONIA-14	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	100	HRV	155	100	Placebo - HRV	0.00	-4.37	2.42
PNEUMONIA-18C	**France**	Placebo	43	100	HRV	83	97.6	Placebo - HRV	2.41	-5.86	8.37
	Germany	Placebo	84	100	HRV	155	100	Placebo - HRV	0.00	-4.37	2.42
PNEUMONIA-19F	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	100	HRV	155	100	Placebo - HRV	0.00	-4.37	2.42
PNEUMONIA-23F	**France**	Placebo	43	100	HRV	83	98.8	Placebo - HRV	1.20	-7.03	6.51
	Germany	Placebo	84	95.2	HRV	155	94.8	Placebo - HRV	0.40	-6.90	6.00

N = number of subjects with available results

% = percentage of subjects with IGS/S.PNEUMONIA-4 concentration ≥ 0.05 µg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 226 Difference in seropositivity rates post Dose 3 of Prevenar between placebo and HRV groups, for *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F antibody concentration ≥ 0.2 mcg/ml - ATP cohort for immunogenicity

								Difference in seropositivity rate			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
PNEUMONIA-4	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	100	HRV	155	100	Placebo - HRV	0.00	-4.37	2.42
PNEUMONIA-6B	**France**	Placebo	43	88.4	HRV	83	83.1	Placebo - HRV	5.24	-9.19	17.12
	Germany	Placebo	84	70.2	HRV	155	69.0	Placebo - HRV	1.21	-11.33	12.94
PNEUMONIA-9V	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	100	HRV	155	99.4	Placebo - HRV	0.65	-3.74	3.56
PNEUMONIA-14	**France**	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	84	98.8	HRV	155	99.4	Placebo - HRV	-0.55	-5.84	2.52
PNEUMONIA-18C	**France**	Placebo	43	100	HRV	83	96.4	Placebo - HRV	3.61	-4.69	10.10
	Germany	Placebo	84	97.6	HRV	155	99.4	Placebo - HRV	-1.74	-7.68	1.52
PNEUMONIA-19F	**France**	Placebo	43	97.7	HRV	83	97.6	Placebo - HRV	0.08	-9.83	6.44
	Germany	Placebo	84	100	HRV	155	99.4	Placebo - HRV	0.65	-3.74	3.56
PNEUMONIA-23F	**France**	Placebo	43	95.3	HRV	83	91.6	Placebo - HRV	3.78	-7.77	12.71
	Germany	Placebo	84	84.5	HRV	155	88.4	Placebo - HRV	-3.86	-14.05	4.81

N = number of subjects with available results

% = percentage of subjects with IGS/S.PNEUMONIA concentration ≥ 0.2 μg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 227 Difference in seroprotection rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-diphtheria - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Czech Republic	Placebo	89	100	HRV	182	100	Placebo - HRV	0.00	-4.14	2.07
France	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
Germany	Placebo	84	98.8	HRV	155	95.5	Placebo - HRV	3.33	-2.23	8.06
Spain	Placebo	91	100	HRV	188	100	Placebo - HRV	0.00	-4.05	2.00

N = number of subjects with available results

% = percentage of subjects with anti-diphtheria concentration ≥ 0.1 IU/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 228 Difference in seroprotection rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-tetanus - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Czech Republic	Placebo	90	100	HRV	182	100	Placebo - HRV	0.00	-4.09	2.07
France	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
Germany	Placebo	84	100	HRV	155	98.1	Placebo - HRV	1.94	-2.47	5.54
Spain	Placebo	90	100	HRV	188	99.5	Placebo - HRV	0.53	-3.57	2.95

N = number of subjects with available results

% = percentage of subjects with anti-tetanus concentration ≥ 0.1 IU/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 229 Difference in seropositivity rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-PT, anti-FHA and anti-PRN - ATP cohort for immunogenicity

								Difference in seropositivity rate			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-PT	**Czech Republic**	Placebo	90	100	HRV	181	99.4	Placebo - HRV	0.55	-3.55	3.06
	France	Placebo	43	100	HRV	83	100	Placebo - HRV	0.00	-8.20	4.42
	Germany	Placebo	82	93.9	HRV	153	91.5	Placebo - HRV	2.40	-5.73	9.05
	Spain	Placebo	91	100	HRV	188	99.5	Placebo - HRV	0.53	-3.53	2.95
Anti-FHA	**Czech Republic**	Placebo	90	100	HRV	182	100	Placebo - HRV	0.00	-4.09	2.07
	France	Placebo	43	100	HRV	82	100	Placebo - HRV	0.00	-8.20	4.48
	Germany	Placebo	84	97.6	HRV	155	98.1	Placebo - HRV	-0.45	-6.49	3.57
	Spain	Placebo	91	100	HRV	188	100	Placebo - HRV	0.00	-4.05	2.00
Anti-PRN	**Czech Republic**	Placebo	90	100	HRV	182	100	Placebo - HRV	0.00	-4.09	2.07
	France	Placebo	43	100	HRV	82	100	Placebo - HRV	0.00	-8.20	4.48
	Germany	Placebo	84	97.6	HRV	155	94.8	Placebo - HRV	2.78	-3.53	7.92
	Spain	Placebo	91	100	HRV	188	100	Placebo - HRV	0.00	-4.05	2.00

N = number of subjects with available results

% = percentage of subjects with anti-PT, anti-FHA, anti-PRN concentration ≥ 5 EL.U/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 230 Difference in seroprotection rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-HBs - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Czech Republic	Placebo	90	97.8	HRV	181	97.8	Placebo - HRV	-0.01	-5.70	3.74
Germany	Placebo	82	79.3	HRV	152	78.3	Placebo - HRV	0.98	-10.62	11.41
Spain	Placebo	90	94.4	HRV	187	98.4	Placebo - HRV	-3.95	-10.88	0.25

N = number of subjects with available results

% = percentage of subjects with anti-HBs concentration ≥ 10 mIU/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 231 Difference in seroprotection rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-polio type 1, anti-polio type 2 and anti-polio type 3 - ATP cohort for immunogenicity

								Difference in seroprotection rate			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-poliovirus type 1	**Czech Republic**	Placebo	65	100	HRV	122	100	Placebo - HRV	0.00	-5.58	3.05
	France	Placebo	30	96.7	HRV	44	100	Placebo - HRV	-3.33	-16.67	4.86
	Germany	Placebo	60	91.7	HRV	108	91.7	Placebo - HRV	0.00	-10.53	8.38
	Spain	Placebo	58	100	HRV	123	100	Placebo - HRV	0.00	-6.21	3.03
Anti-poliovirus type 2	**Czech Republic**	Placebo	59	96.6	HRV	124	100	Placebo - HRV	-3.39	-11.54	-0.32
	France	Placebo	29	93.1	HRV	44	93.2	Placebo - HRV	-0.08	-15.98	12.64
	Germany	Placebo	62	82.3	HRV	110	83.6	Placebo - HRV	-1.38	-14.16	9.77
	Spain	Placebo	57	100	HRV	118	99.2	Placebo - HRV	0.85	-5.48	4.64
Anti-poliovirus type 3	**Czech Republic**	Placebo	65	100	HRV	114	100	Placebo - HRV	0.00	-5.58	3.26
	France	Placebo	30	100	HRV	44	100	Placebo - HRV	0.00	-11.35	8.03
	Germany	Placebo	59	88.1	HRV	109	89.9	Placebo - HRV	-1.77	-13.37	7.62
	Spain	Placebo	53	100	HRV	120	97.5	Placebo - HRV	2.50	-4.31	7.09

N = number of subjects with available results

% = percentage of subjects with anti-polio types 1, 2 and 3 titer $\geq$ 8 ED50

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 232 Difference in seroprotection rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-PRP concentration ≥0.15 mcg/ml - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Czech Republic	Placebo	90	100	HRV	182	98.4	Placebo - HRV	1.65	-2.47	4.73
France	Placebo	43	97.7	HRV	80	95.0	Placebo - HRV	2.67	-7.45	10.28
Germany	Placebo	83	81.9	HRV	154	86.4	Placebo - HRV	-4.44	-15.16	4.89
Spain	Placebo	91	93.4	HRV	187	97.3	Placebo - HRV	-3.92	-11.19	0.92

N = number of subjects with available results

% = percentage of subjects with anti-RP concentration ≥ 0.15 μg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 233 Difference in seroprotection rates post Dose 3 of childhood vaccinations between placebo and HRV groups, for anti-PRP concentration ≥1 mcg/ml - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Czech Republic	Placebo	90	72.2	HRV	182	76.4	Placebo - HRV	-4.15	-15.70	6.49
France	Placebo	43	60.5	HRV	80	57.5	Placebo - HRV	2.97	-15.32	20.40
Germany	Placebo	83	60.2	HRV	154	60.4	Placebo - HRV	-0.15	-13.28	12.58
Spain	Placebo	91	78.0	HRV	187	79.1	Placebo - HRV	-1.12	-12.04	8.64

N = number of subjects with available results

% = percentage of subjects with anti-PRP concentration ≥ 1 μg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 234 Ratio of anti-PSC antibody GMCs, post Dose 3 of Meningitec between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Spain	Placebo	91	8.76	HRV	187	7.63	Placebo / HRV	1.15	0.95	1.39

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 235 Ratio of anti-SBA-MENC antibody GMCs, post Dose 3 of Meningitec between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Spain	Placebo	90	1769.1	HRV	184	1455.4	Placebo / HRV	1.22	0.91	1.62

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 236 Ratio of GMCs for antibodies to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, post Dose 3 of Prevenar between placebo and HRV groups - ATP cohort for immunogenicity

								GMC ratio			
										95 % CI	
Antibody	Country	Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
PNEUMONIA-4	France	Placebo	43	2.39	HRV	83	2.40	Placebo / HRV	1.00	0.76	1.30
	Germany	Placebo	84	3.11	HRV	155	3.17	Placebo / HRV	0.98	0.79	1.22
PNEUMONIA-6B	France	Placebo	43	0.65	HRV	83	0.79	Placebo / HRV	0.82	0.51	1.33
	Germany	Placebo	84	0.49	HRV	155	0.48	Placebo / HRV	1.03	0.66	1.60
PNEUMONIA-9V	France	Placebo	43	2.39	HRV	83	2.42	Placebo / HRV	0.99	0.76	1.28
	Germany	Placebo	84	2.65	HRV	155	2.94	Placebo / HRV	0.90	0.71	1.14
PNEUMONIA-14	France	Placebo	43	5.29	HRV	83	4.68	Placebo / HRV	1.13	0.80	1.60
	Germany	Placebo	84	3.89	HRV	155	4.59	Placebo / HRV	0.85	0.64	1.13
PNEUMONIA-18C	France	Placebo	43	2.56	HRV	83	2.47	Placebo / HRV	1.04	0.70	1.53
	Germany	Placebo	84	3.31	HRV	155	3.40	Placebo / HRV	0.97	0.74	1.29
PNEUMONIA-19F	France	Placebo	43	2.75	HRV	83	2.85	Placebo / HRV	0.97	0.67	1.39
	Germany	Placebo	84	3.51	HRV	155	3.62	Placebo / HRV	0.97	0.74	1.27
PNEUMONIA-23F	France	Placebo	43	1.35	HRV	83	1.25	Placebo / HRV	1.08	0.70	1.65
	Germany	Placebo	84	1.21	HRV	155	1.31	Placebo / HRV	0.92	0.60	1.41

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 237 Ratio of anti-diphtheria antibody GMCs, post Dose 3 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Czech Republic	Placebo	89	2.694	HRV	182	2.321	Placebo / HRV	1.16	0.97	1.39
France	Placebo	43	1.118	HRV	83	1.168	Placebo / HRV	0.96	0.68	1.34
Germany	Placebo	84	1.350	HRV	155	1.389	Placebo / HRV	0.97	0.70	1.34
Spain	Placebo	91	6.830	HRV	188	6.653	Placebo / HRV	1.03	0.87	1.21

GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 238 Ratio of anti-tetanus antibody GMCs, post Dose 3 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Czech Republic	Placebo	90	1.789	HRV	182	1.918	Placebo / HRV	0.93	0.75	1.16
France	Placebo	43	1.384	HRV	83	1.353	Placebo / HRV	1.02	0.76	1.38
Germany	Placebo	84	1.150	HRV	155	1.094	Placebo / HRV	1.05	0.79	1.40
Spain	Placebo	90	1.669	HRV	188	1.665	Placebo / HRV	1.00	0.81	1.24

GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 239 Ratio of anti-PT, anti-FHA, anti-PRN antibody GMCs, post Dose 3 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

								GMC ratio			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Anti-PT	**Czech Republic**	Placebo	90	53.4	HRV	181	55.6	Placebo / HRV	0.96	0.82	1.13
	France	Placebo	43	46.3	HRV	83	42.1	Placebo / HRV	1.10	0.89	1.35
	Germany	Placebo	82	28.4	HRV	153	30.2	Placebo / HRV	0.94	0.72	1.23
	Spain	Placebo	91	45.1	HRV	188	42.9	Placebo / HRV	1.05	0.90	1.23
Anti-FHA	**Czech Republic**	Placebo	90	214.8	HRV	182	215.8	Placebo / HRV	1.00	0.80	1.23
	France	Placebo	43	180.3	HRV	82	176.2	Placebo / HRV	1.02	0.75	1.40
	Germany	Placebo	84	97.5	HRV	155	110.3	Placebo / HRV	0.88	0.71	1.11
	Spain	Placebo	91	161.1	HRV	188	159.2	Placebo / HRV	1.01	0.86	1.19
Anti-PRN	**Czech Republic**	Placebo	90	113.8	HRV	182	112.8	Placebo / HRV	1.01	0.83	1.23
	France	Placebo	43	110.7	HRV	82	101.4	Placebo / HRV	1.09	0.79	1.50
	Germany	Placebo	84	75.6	HRV	155	73.6	Placebo / HRV	1.03	0.73	1.45
	Spain	Placebo	91	106.7	HRV	188	105.3	Placebo / HRV	1.01	0.83	1.24

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 240 Ratio of anti-HBs antibody GMCs, post Dose 3 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Czech Republic	Placebo	90	329.4	HRV	181	408.6	Placebo / HRV	0.81	0.56	1.16
Germany	Placebo	82	117.7	HRV	152	143.2	Placebo / HRV	0.82	0.47	1.43
Spain	Placebo	90	861.3	HRV	187	832.5	Placebo / HRV	1.03	0.70	1.54

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 241 Ratio of anti-polio antibody GMCs, post Dose 3 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

								GMC ratio			
										95 % CI	
Antibody	Country	Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Anti-polio type 1	Czech Republic	Placebo	65	370.0	HRV	122	445.5	Placebo / HRV	0.83	0.55	1.26
	France	Placebo	30	142.3	HRV	44	89.7	Placebo / HRV	1.59	0.77	3.25
	Germany	Placebo	60	85.4	HRV	108	119.1	Placebo / HRV	0.72	0.39	1.30
	Spain	Placebo	58	590.9	HRV	123	661.7	Placebo / HRV	0.89	0.61	1.30
Anti-polio type 2	Czech Republic	Placebo	59	269.8	HRV	124	376.5	Placebo / HRV	0.72	0.44	1.17
	France	Placebo	29	49.8	HRV	44	52.5	Placebo / HRV	0.95	0.45	2.00
	Germany	Placebo	62	51.7	HRV	110	62.0	Placebo / HRV	0.83	0.46	1.51
	Spain	Placebo	57	267.1	HRV	118	402.6	Placebo / HRV	0.66	0.42	1.04
Anti-polio type 3	Czech Republic	Placebo	65	970.6	HRV	114	1153.0	Placebo / HRV	0.84	0.55	1.29
	France	Placebo	30	189.8	HRV	44	217.3	Placebo / HRV	0.87	0.39	1.95
	Germany	Placebo	59	107.2	HRV	109	211.5	Placebo / HRV	0.51	0.25	1.03
	Spain	Placebo	53	880.8	HRV	120	1126.3	Placebo / HRV	0.78	0.48	1.27

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 242 Ratio of anti-PRP antibody GMCs, post Dose 3 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Czech Republic	Placebo	90	2.264	HRV	182	2.862	Placebo / HRV	0.79	0.57	1.10
France	Placebo	43	1.385	HRV	80	1.388	Placebo / HRV	1.00	0.60	1.66
Germany	Placebo	83	1.098	HRV	154	1.344	Placebo / HRV	0.82	0.52	1.29
Spain	Placebo	91	2.607	HRV	187	2.796	Placebo / HRV	0.93	0.64	1.36

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

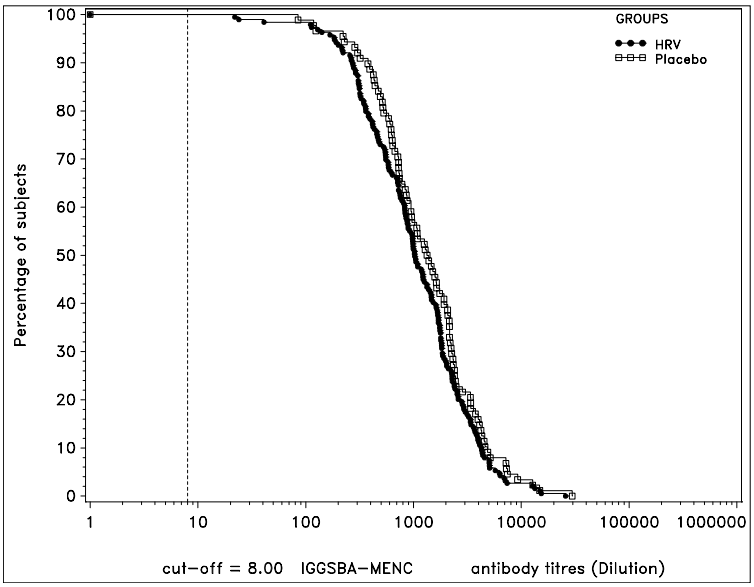
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 243 Seropositivity rates and GMTs for anti-SBA-MenC antibodies post Dose 2 of Meningitec - ATP cohort for immunogenicity

				≥ 8 1/DIL.				≥ 128 1/DIL.				GMT		
						95% CI				95% CI			95% CI	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Spain	**HRV**	**PII(M3-M4)**	189	189	100	98.1	100	184	97.4	93.9	99.1	1049.9	889.3	1239.6
	Placebo	**PII(M3-M4)**	88	88	100	95.9	100	85	96.6	90.4	99.3	1336.0	1059.1	1685.2

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of Meningitec (Visit 3)

Supplement 244 Reverse cumulative curves for anti-SBA-MenC antibody concentrations post Dose 2 of Meningitec – Spain – ATP cohort for immunogenicity

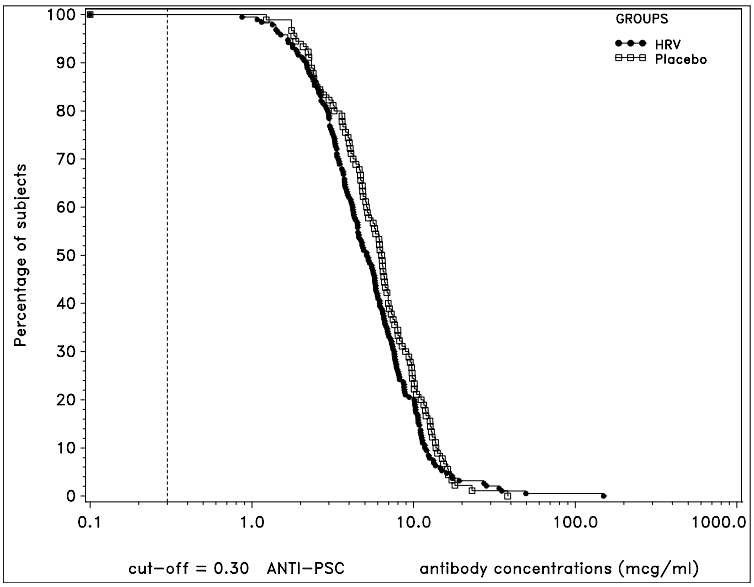


Supplement 245 Seropositivity rates and GMCs for anti-PSC antibodies post Dose 2 of Meningitec - ATP cohort for immunogenicity

				≥ 0.3 µg/ml				≥ 2 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Spain	**HRV**	**PII(M3-M4)**	190	190	100	98.1	100	174	91.6	86.7	95.1	5.25	4.72	5.84
	Placebo	**PII(M3-M4)**	90	90	100	96.0	100	85	94.4	87.5	98.2	6.07	5.27	6.99

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of Meningitec (Visit 3)

Supplement 246 Reverse cumulative curves for anti-PSC antibody concentrations post Dose 2 of Meningitec – Spain – ATP cohort for immunogenicity

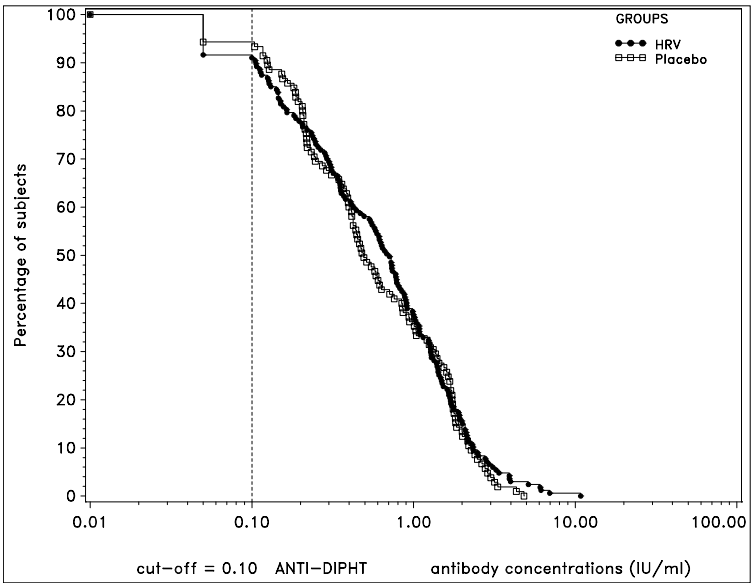


Supplement 247 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 2 of childhood vaccinations – ATP cohort for immunogenicity

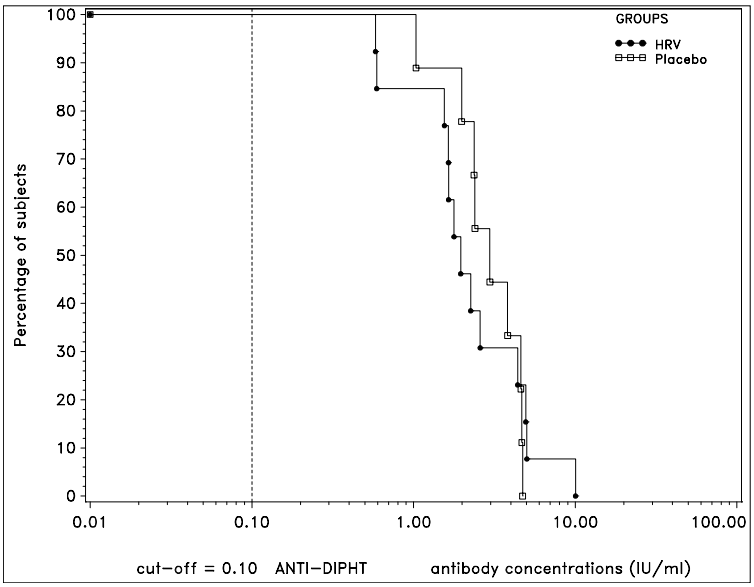
					≥ 0.1 IU/ml				GMC (IU/ml)		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	Finland	HRV	PII(M3-M4)	167	153	91.6	86.3	95.3	0.569	0.470	0.689
		Placebo	PII(M3-M4)	105	99	94.3	88.0	97.9	0.550	0.441	0.687
	Italy	HRV	PII(M3-M4)	13	13	100	75.3	100	2.223	1.358	3.640
		Placebo	PII(M3-M4)	9	9	100	66.4	100	2.876	1.950	4.240
	Spain	HRV	PII(M3-M4)	191	191	100	98.1	100	3.613	3.213	4.064
		Placebo	PII(M3-M4)	90	90	100	96.0	100	4.011	3.323	4.842
Anti-tetanus	Finland	HRV	PII(M3-M4)	167	167	100	97.8	100	1.206	1.043	1.394
		Placebo	PII(M3-M4)	105	105	100	96.5	100	1.351	1.133	1.611
	Italy	HRV	PII(M3-M4)	13	13	100	75.3	100	2.278	1.395	3.719
		Placebo	PII(M3-M4)	9	9	100	66.4	100	2.765	1.363	5.608
	Spain	HRV	PII(M3-M4)	191	189	99.0	96.3	99.9	0.848	0.737	0.975
		Placebo	PII(M3-M4)	90	89	98.9	94.0	100	0.796	0.641	0.987

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of childhood vaccination (Visit 3)

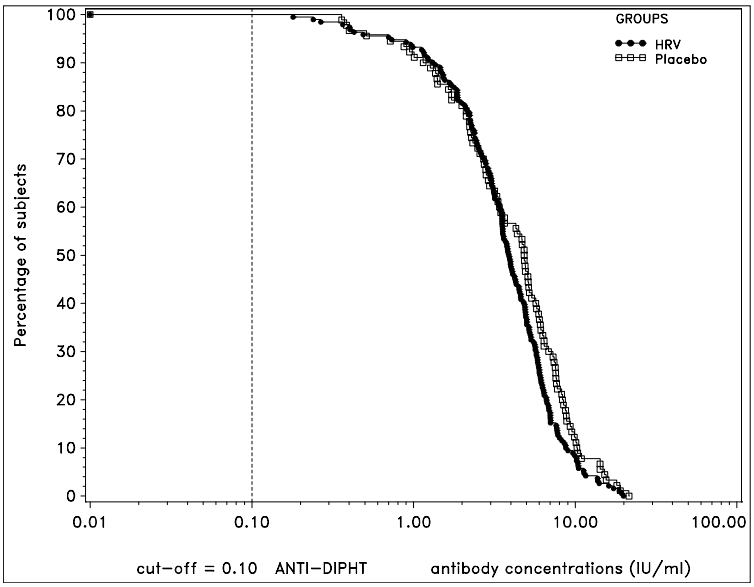
Supplement 248 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



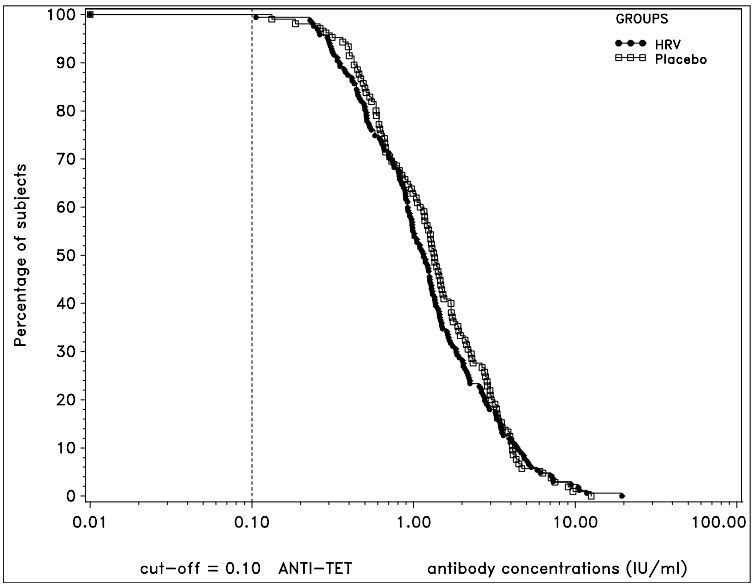
Supplement 249 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



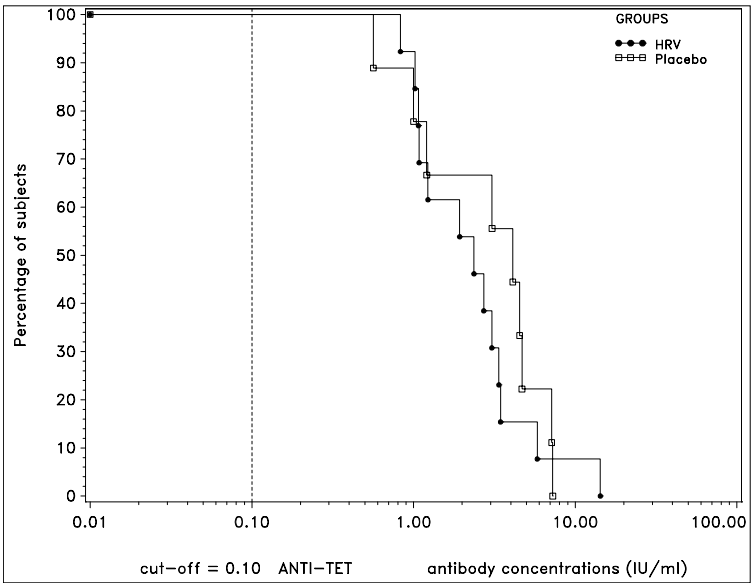
Supplement 250 Reverse cumulative curves for anti-diphtheria antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity



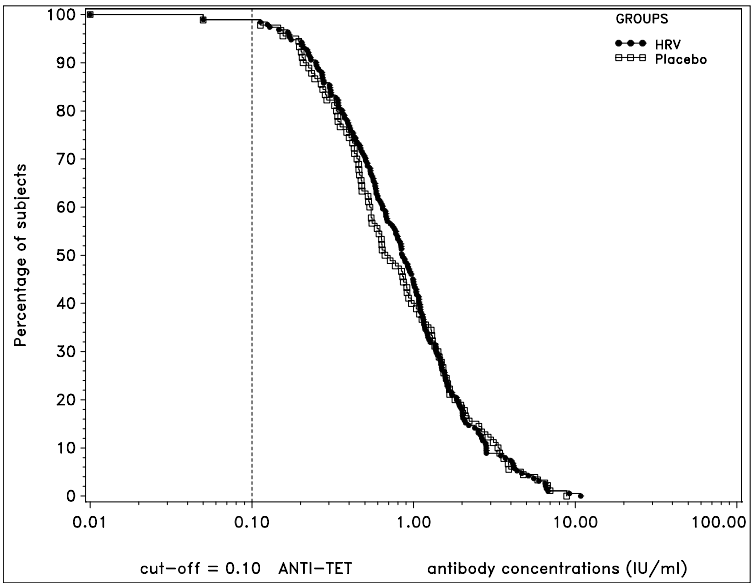
Supplement 251 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



Supplement 252 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



Supplement 253 Reverse cumulative curves for anti-tetanus antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity

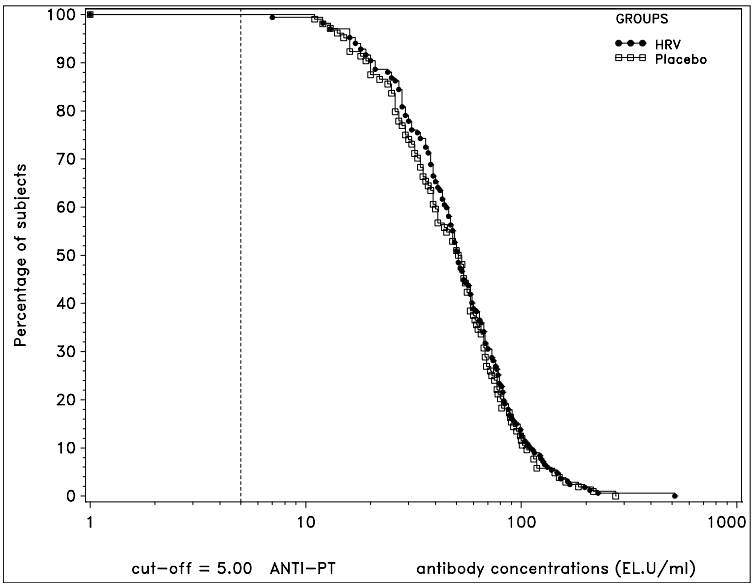


Supplement 254 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 2 of childhood vaccinations - ATP cohort for immunogenicity

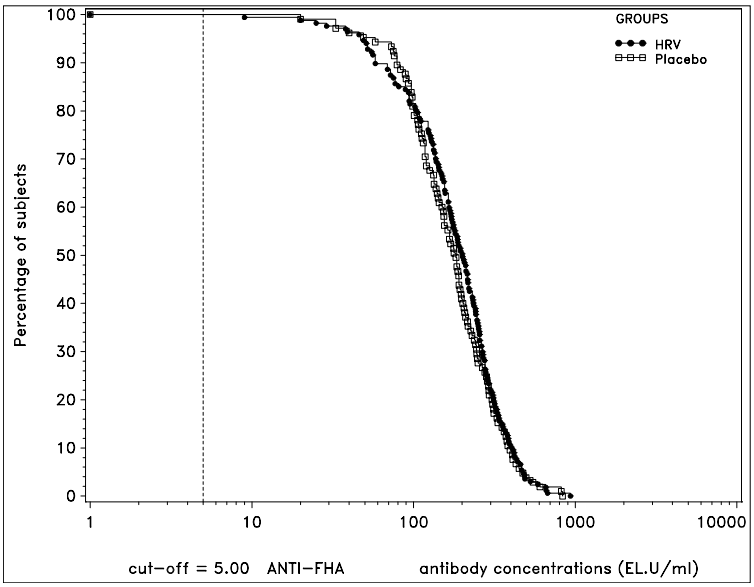
					≥ 5 EL.U/ml				GMC (EL.U/ml)		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Finland	HRV	PII(M3-M4)	167	167	100	97.8	100	50.9	46.1	56.3
		Placebo	PII(M3-M4)	104	104	100	96.5	100	47.8	42.1	54.4
	Italy	HRV	PII(M3-M4)	13	13	100	75.3	100	47.3	25.2	89.0
		Placebo	PII(M3-M4)	8	8	100	63.1	100	44.0	27.4	70.6
	Spain	HRV	PII(M3-M4)	190	187	98.4	95.5	99.7	27.0	24.1	30.2
		Placebo	PII(M3-M4)	90	90	100	96.0	100	28.5	25.0	32.4
Anti-FHA	Finland	HRV	PII(M3-M4)	167	167	100	97.8	100	179.0	160.1	200.1
		Placebo	PII(M3-M4)	105	105	100	96.5	100	173.8	152.7	197.9
	Italy	HRV	PII(M3-M4)	13	13	100	75.3	100	241.8	152.6	383.2
		Placebo	PII(M3-M4)	9	9	100	66.4	100	152.7	99.6	234.2
	Spain	HRV	PII(M3-M4)	191	191	100	98.1	100	95.2	85.3	106.3
		Placebo	PII(M3-M4)	90	90	100	96.0	100	97.0	82.4	114.3
Anti-PRN	Finland	HRV	PII(M3-M4)	166	164	98.8	95.7	99.9	77.2	64.2	93.0
		Placebo	PII(M3-M4)	103	102	99.0	94.7	100	97.9	78.2	122.5
	Italy	HRV	PII(M3-M4)	13	13	100	75.3	100	124.0	59.8	257.3
		Placebo	PII(M3-M4)	9	9	100	66.4	100	168.9	117.7	242.4
	Spain	HRV	PII(M3-M4)	191	185	96.9	93.3	98.8	49.0	41.8	57.4
		Placebo	PII(M3-M4)	90	89	98.9	94.0	100	52.4	41.4	66.2

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of childhood vaccination (Visit 3)

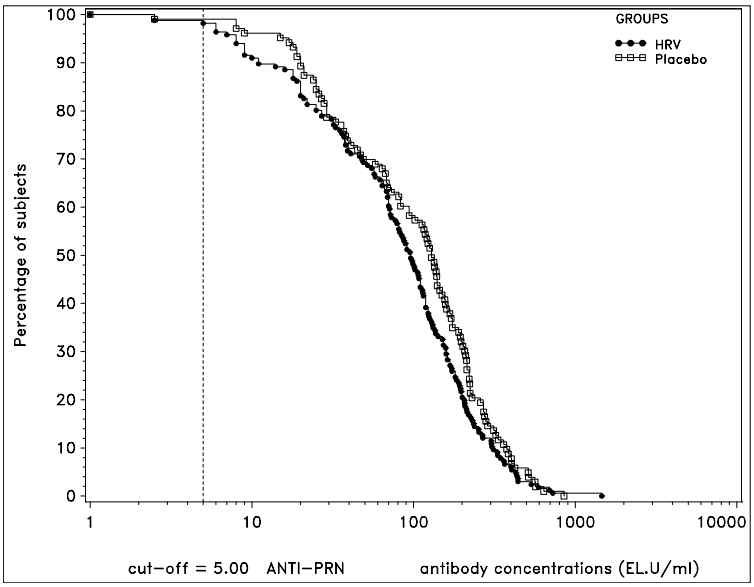
Supplement 255 Reverse cumulative curves for anti-PT antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



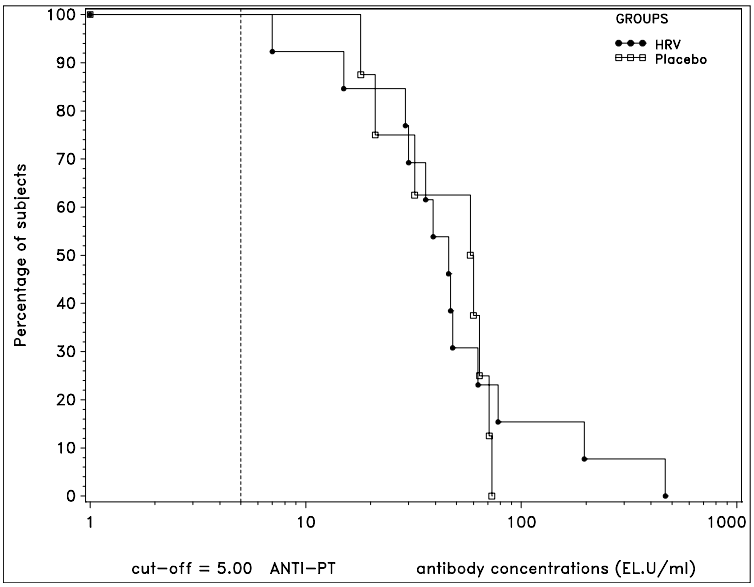
Supplement 256 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



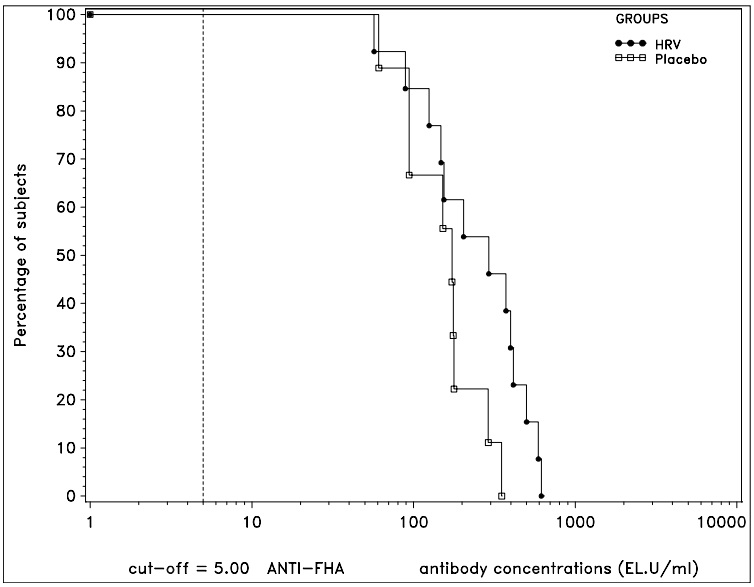
Supplement 257 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



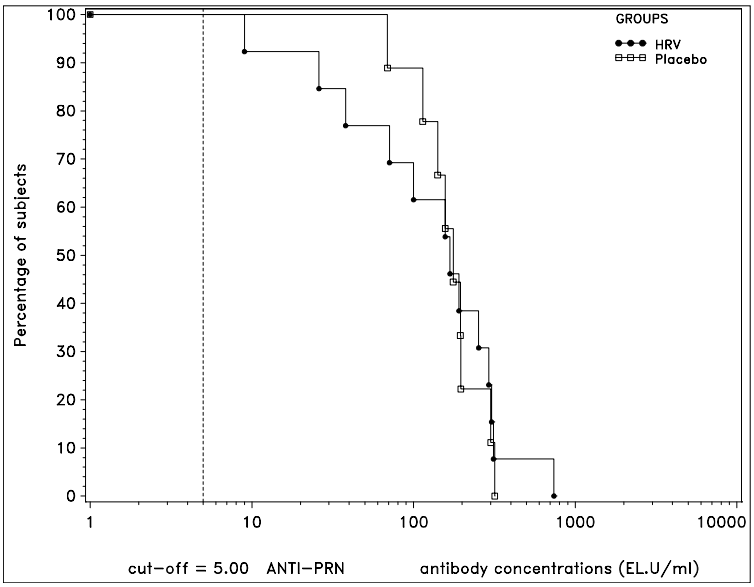
Supplement 258 Reverse cumulative curves for anti-PT antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



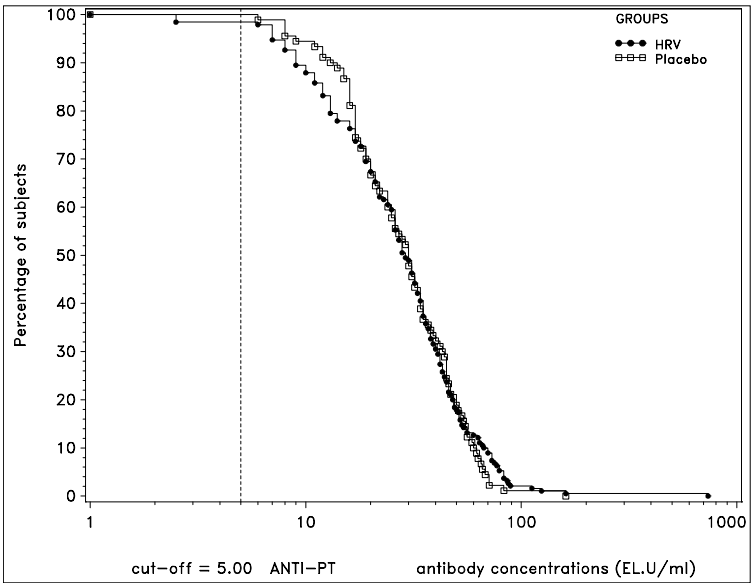
Supplement 259 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



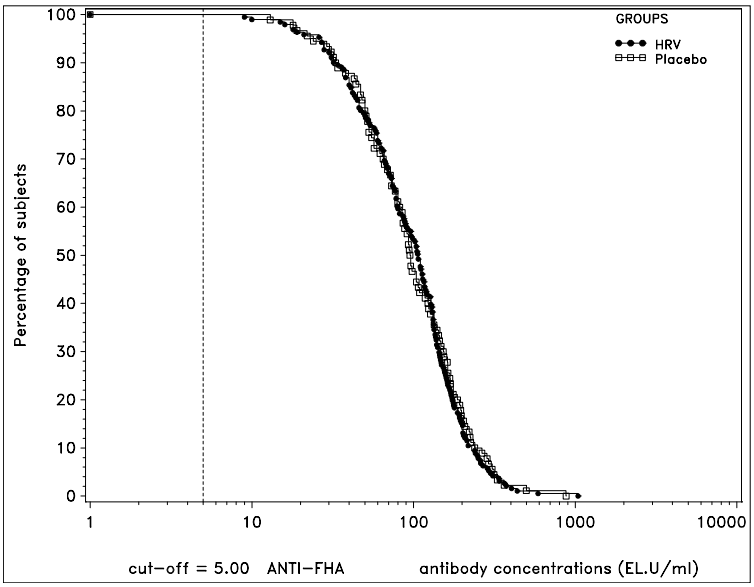
Supplement 260 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



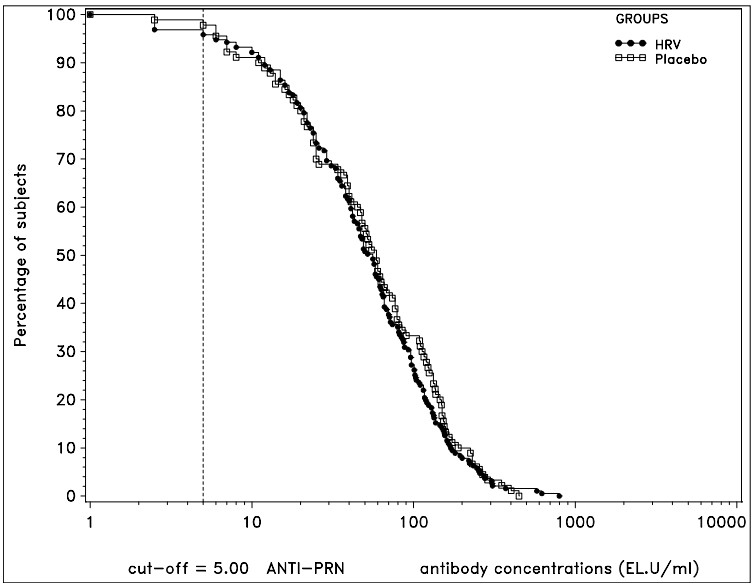
Supplement 261 Reverse cumulative curves for anti-PT antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity



Supplement 262 Reverse cumulative curves for anti-FHA antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity



Supplement 263 Reverse cumulative curves for anti-PRN antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity

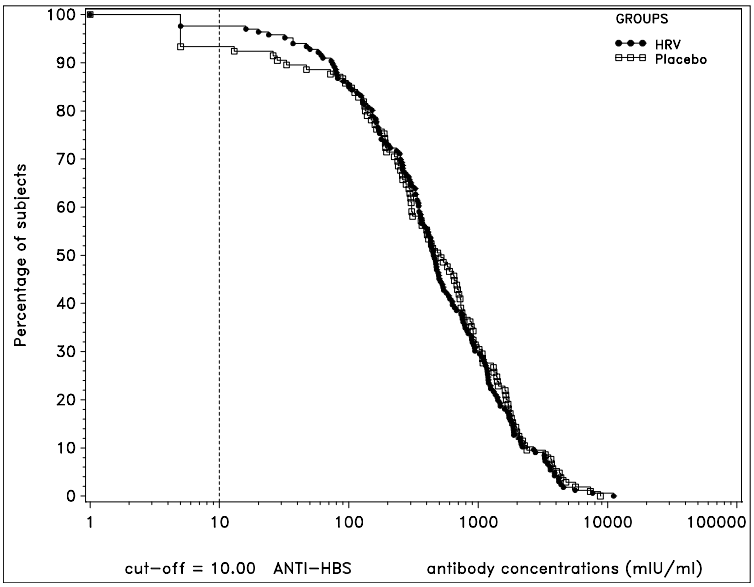


Supplement 264 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 2 of childhood vaccinations - ATP cohort for immunogenicity

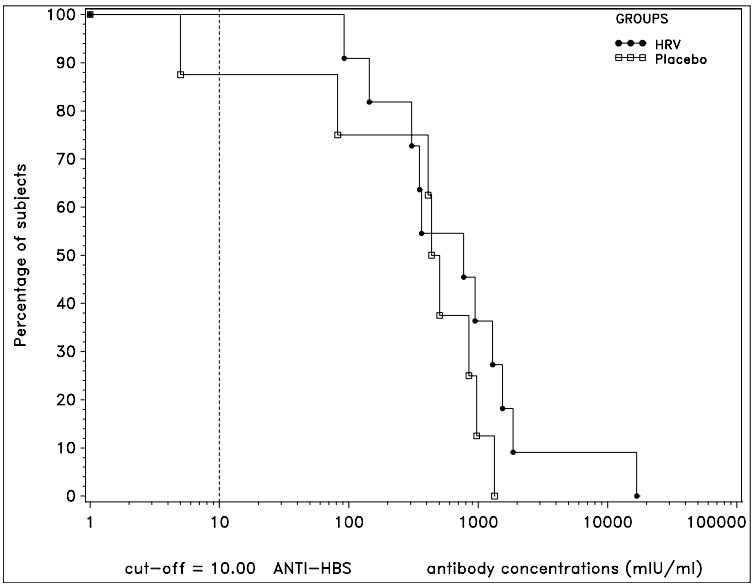
				≥ 10 mIU/ml				GMC (mIU/ml)		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Finland	HRV	PII(M3-M4)	166	162	97.6	93.9	99.3	431.6	345.3	539.4
	Placebo	PII(M3-M4)	105	98	93.3	86.7	97.3	399.7	286.0	558.5
Italy	HRV	PII(M3-M4)	11	11	100	71.5	100	711.9	272.9	1857.1
	Placebo	PII(M3-M4)	8	7	87.5	47.3	99.7	282.6	60.9	1312.8
Spain	HRV	PII(M3-M4)	186	178	95.7	91.7	98.1	334.4	260.4	429.4
	Placebo	PII(M3-M4)	89	84	94.4	87.4	98.2	461.2	315.4	674.4

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of childhood vaccination (Visit 3)

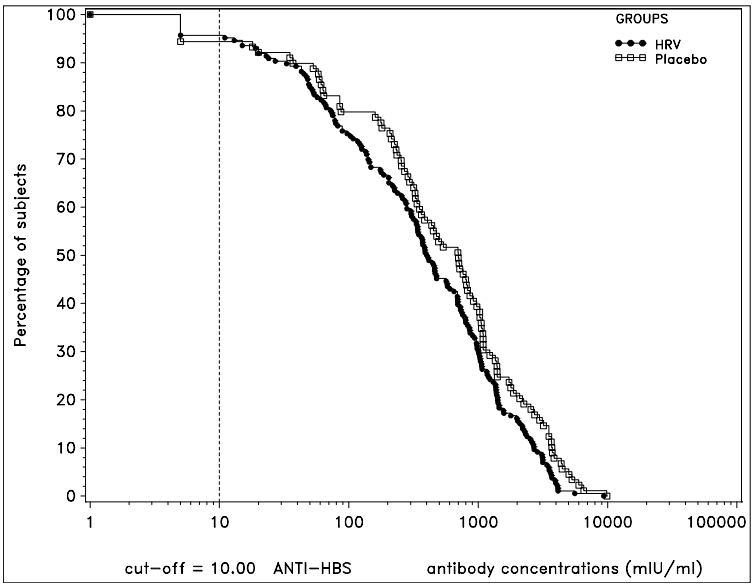
Supplement 265 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



Supplement 266 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



Supplement 267 Reverse cumulative curves for anti-HBs antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity

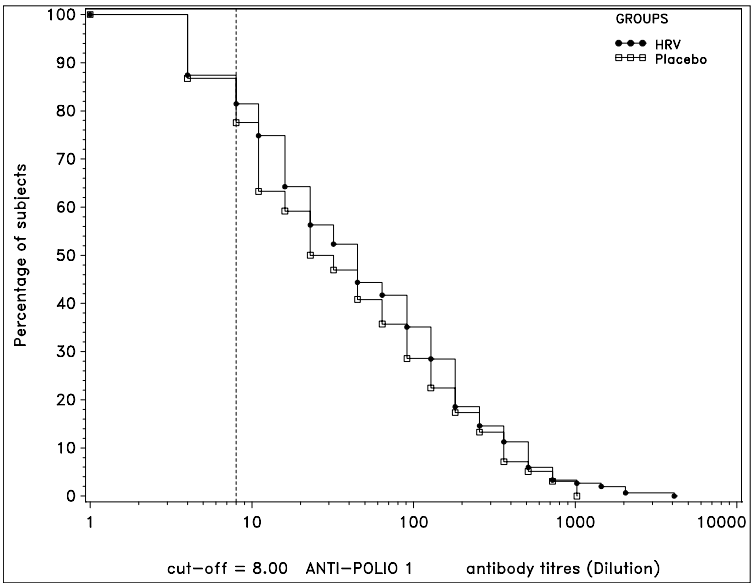


Supplement 268 Seroprotection rates and GMTs for anti-polio 1, anti-polio 2 and anti-polio 3 antibodies post Dose 2 of childhood vaccinations - ATP cohort for immunogenicity

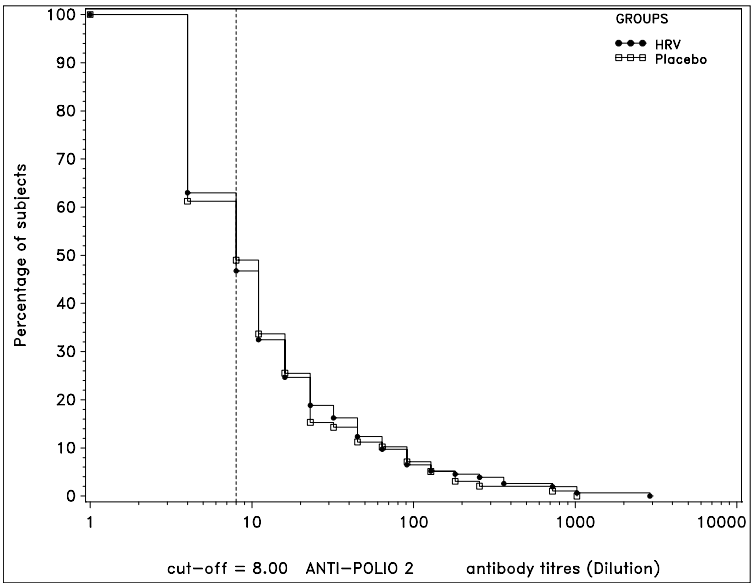
					≥ 8 ED50				GMT		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-polio type 1	Finland	HRV	PII(M3-M4)	151	132	87.4	81.0	92.3	47.3	36.2	61.9
		Placebo	PII(M3-M4)	98	85	86.7	78.4	92.7	37.2	26.9	51.3
	Italy	HRV	PII(M3-M4)	5	5	100	47.8	100	415.8	190.3	908.7
		Placebo	PII(M3-M4)	5	5	100	47.8	100	337.8	115.7	986.2
	Spain	HRV	PII(M3-M4)	119	117	98.3	94.1	99.8	150.7	115.3	197.0
		Placebo	PII(M3-M4)	54	51	94.4	84.6	98.8	137.4	88.9	212.3
Anti-polio type 2	Finland	HRV	PII(M3-M4)	154	97	63.0	54.8	70.6	11.9	9.7	14.7
		Placebo	PII(M3-M4)	98	60	61.2	50.8	70.9	11.4	9.0	14.6
	Italy	HRV	PII(M3-M4)	4	4	100	39.8	100	107.6	9.3	1241.9
		Placebo	PII(M3-M4)	6	6	100	54.1	100	256.0	153.1	428.2
	Spain	HRV	PII(M3-M4)	116	97	83.6	75.6	89.8	49.6	36.5	67.4
		Placebo	PII(M3-M4)	54	45	83.3	70.7	92.1	40.8	25.9	64.2
Anti-polio type 3	Finland	HRV	PII(M3-M4)	151	139	92.1	86.5	95.8	83.2	62.6	110.7
		Placebo	PII(M3-M4)	94	82	87.2	78.8	93.2	49.5	34.3	71.6
	Italy	HRV	PII(M3-M4)	4	3	75.0	19.4	99.4	234.8	1.9	28973.7
		Placebo	PII(M3-M4)	6	6	100	54.1	100	304.4	44.0	2107.4
	Spain	HRV	PII(M3-M4)	117	114	97.4	92.7	99.5	299.6	232.2	386.6
		Placebo	PII(M3-M4)	50	49	98.0	89.4	99.9	150.3	101.0	223.7

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of childhood vaccination (Visit 3)

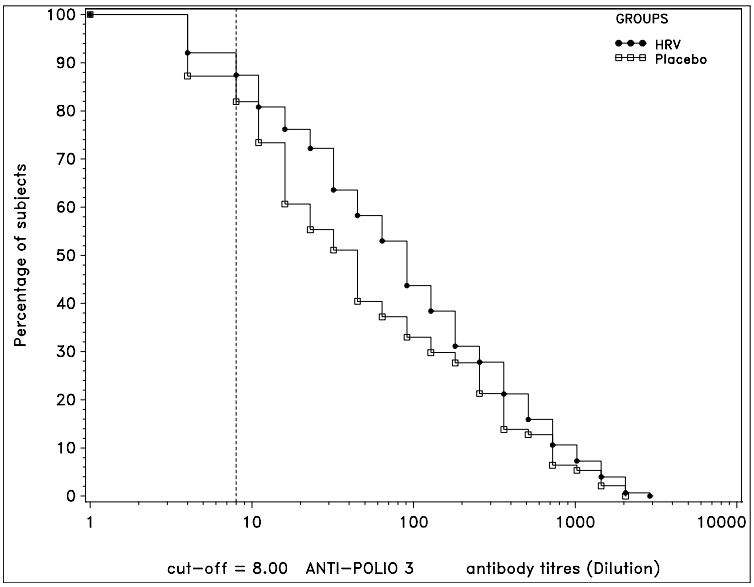
Supplement 269 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



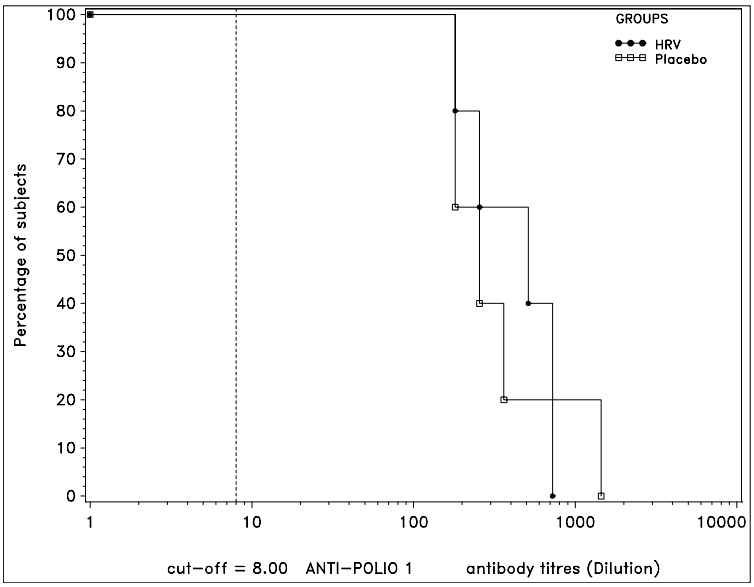
Supplement 270 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



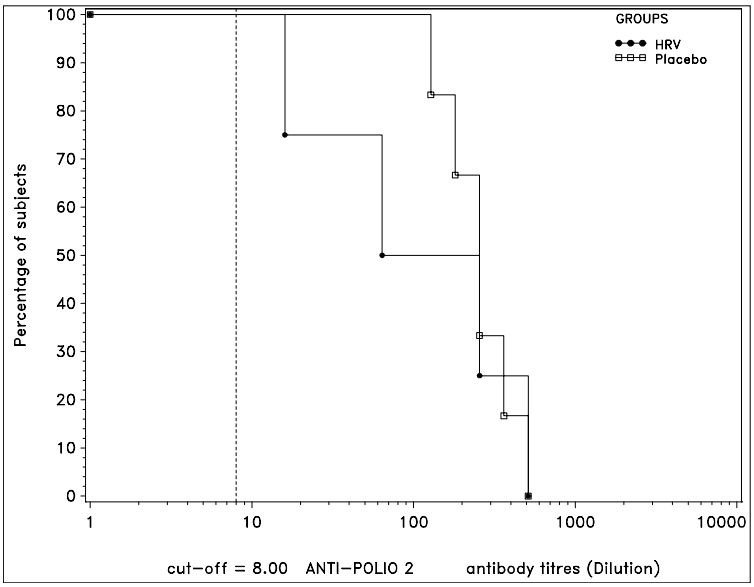
Supplement 271 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



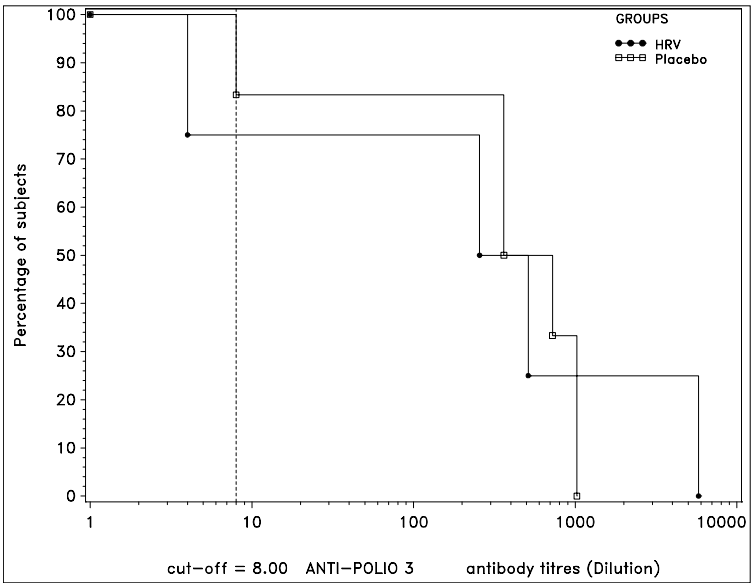
Supplement 272 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



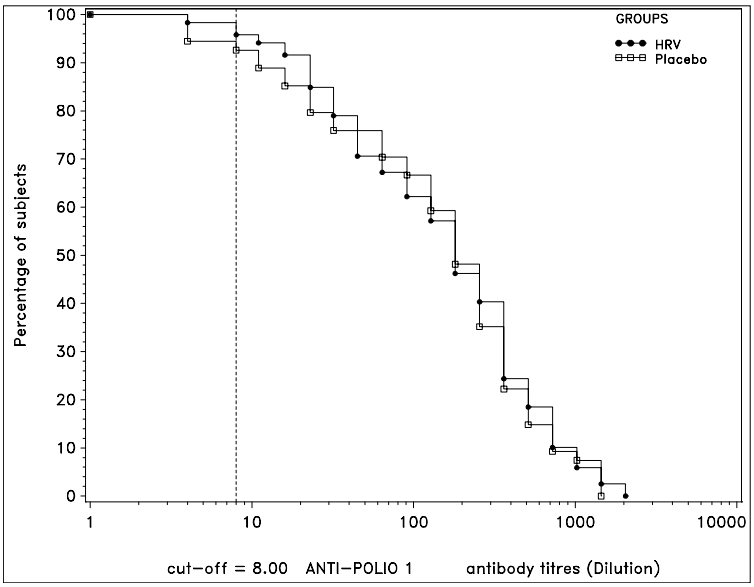
Supplement 273 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 2 of Infanrix Hexa – Italy – ATP cohort for immunogenicity



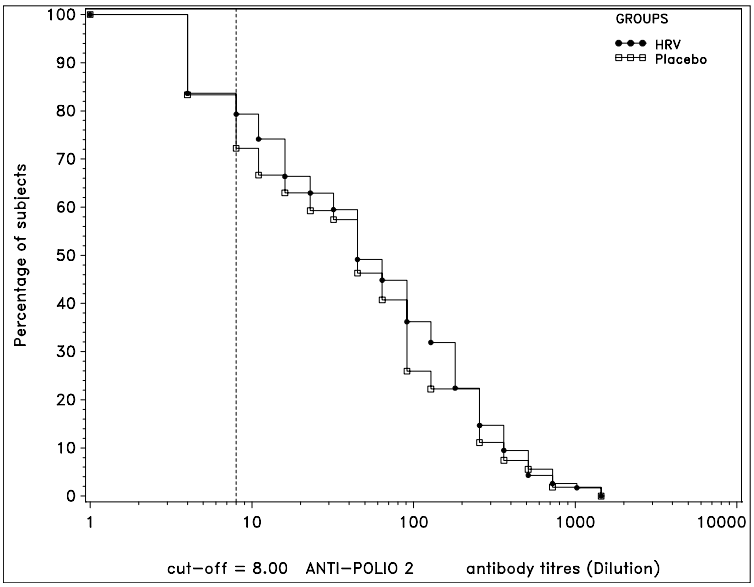
Supplement 274 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



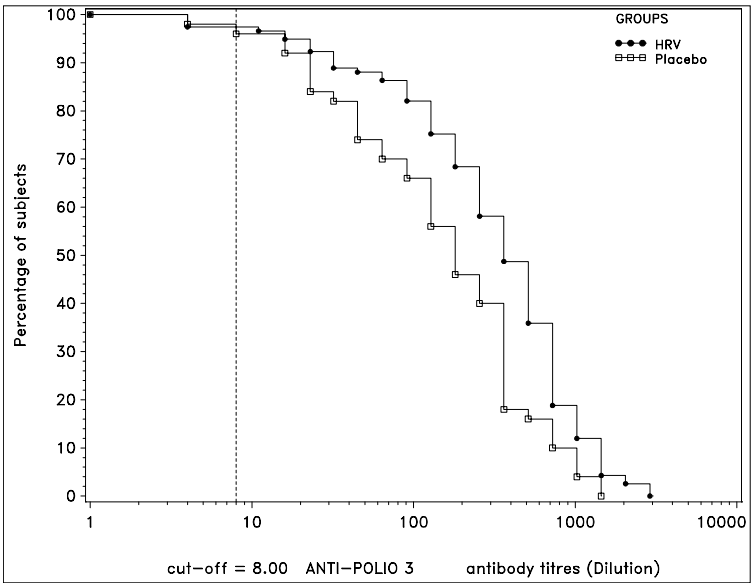
Supplement 275 Reverse cumulative curves for anti-polio type 1 antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity



Supplement 276 Reverse cumulative curves for anti-polio type 2 antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity



Supplement 277 Reverse cumulative curves for anti-polio type 3 antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity

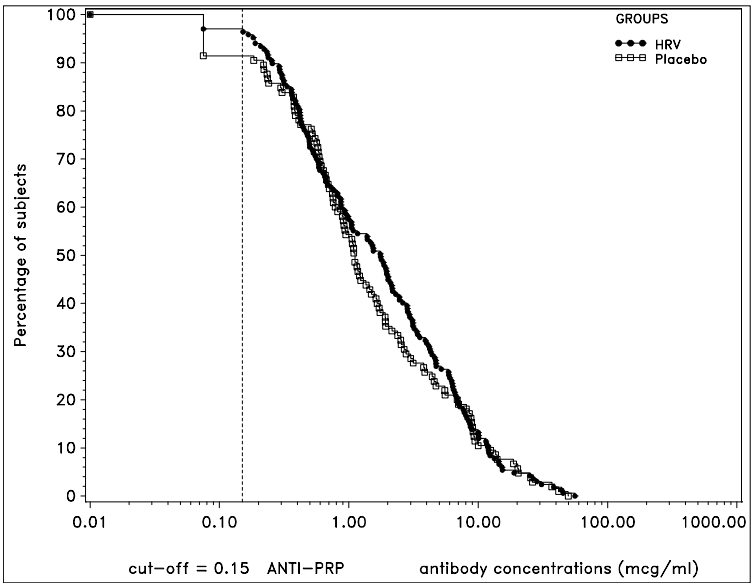


Supplement 278 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 2 of childhood vaccinations - ATP cohort for immunogenicity

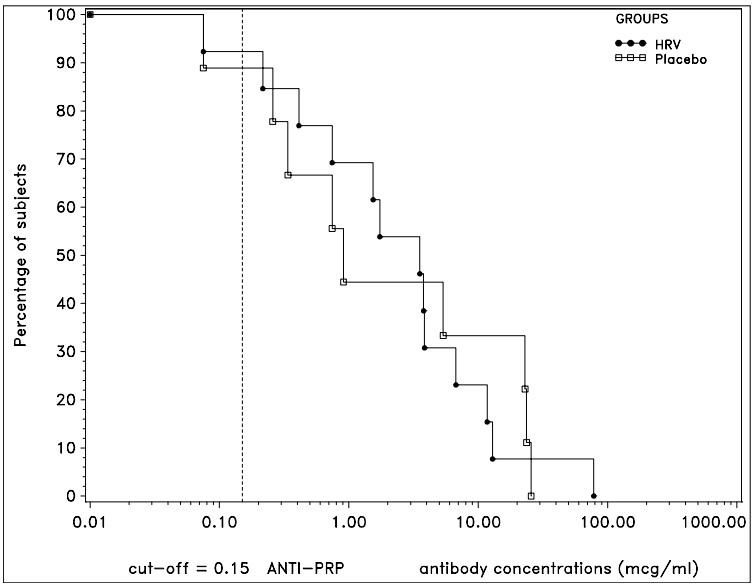
				≥ 0.15 µg/ml				≥ 1.0 µg/ml				GMC (µg/ml)		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Finland	HRV	PII(M3-M4)	167	162	97.0	93.2	99.0	96	57.5	49.6	65.1	1.671	1.326	2.107
	Placebo	PII(M3-M4)	105	96	91.4	84.4	96.0	57	54.3	44.3	64.0	1.365	1.002	1.860
Italy	HRV	PII(M3-M4)	13	12	92.3	64.0	99.8	9	69.2	38.6	90.9	2.313	0.750	7.137
	Placebo	PII(M3-M4)	9	8	88.9	51.8	99.7	4	44.4	13.7	78.8	1.905	0.347	10.461
Spain	HRV	PII(M3-M4)	190	160	84.2	78.2	89.1	87	45.8	38.6	53.2	0.816	0.656	1.014
	Placebo	PII(M3-M4)	90	79	87.8	79.2	93.7	35	38.9	28.8	49.7	0.722	0.530	0.982

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post-Dose 2 of childhood vaccination (Visit 3)

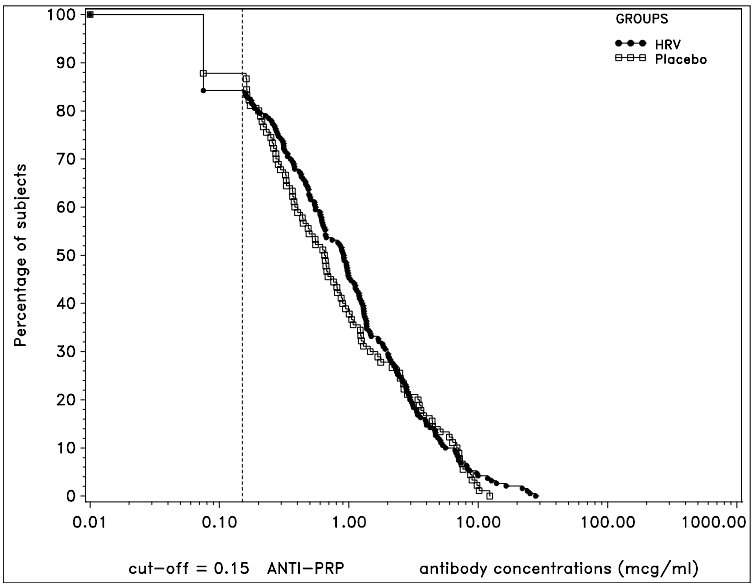
Supplement 279 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 2 of childhood vaccinations – Finland – ATP cohort for immunogenicity



Supplement 280 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 2 of childhood vaccinations – Italy – ATP cohort for immunogenicity



Supplement 281 Reverse cumulative curves for anti-PRP antibody concentrations post Dose 2 of childhood vaccinations – Spain – ATP cohort for immunogenicity



Supplement 282 Difference in seropositivity rates post Dose 2 of Meningitec between placebo and HRV groups, for anti-SBA-MENC titer ≥8 - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	88	100	HRV	189	100	Placebo - HRV	0.00	-4.18	1.99

N = number of subjects with available results

% = percentage of subjects with SBA-MENC titer ≥ 8 1/DIL.

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 283 Difference in seropositivity rates post Dose 2 of Meningitec between placebo and HRV groups, for anti-SBA-MENC titer ≥128 - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	88	96.6	HRV	189	97.4	Placebo - HRV	-0.76	-7.10	3.34

N = number of subjects with available results

% = percentage of subjects with SBA-MENC titer ≥ 128 1/DIL.

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 284 Difference in seropositivity rates post Dose 2 of Meningitec between placebo and HRV groups, for Anti-PSC concentration ≥0.3 mcg/ml - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	90	100	HRV	190	100	Placebo - HRV	0.00	-4.09	1.98

N = number of subjects with available results

% = percentage of subjects with anti-PSC concentration ≥ 0.3 μg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 285 Difference in seropositivity rates post Dose 2 of Meningitec between placebo and HRV groups, for Anti-PSC concentration ≥2 mcg/ml - ATP cohort for immunogenicity

							Difference in seropositivity rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Spain	Placebo	90	94.4	HRV	190	91.6	Placebo - HRV	2.87	-4.58	8.78

N = number of subjects with available results

% = percentage of subjects with anti-PSC concentration ≥ 2 μg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 286 Difference in seroprotection rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-diphtheria - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Finland	Placebo	105	94.3	HRV	167	91.6	Placebo - HRV	2.67	-4.32	8.83
Italy	Placebo	9	100	HRV	13	100	Placebo - HRV	0.00	-29.91	22.81
Spain	Placebo	90	100	HRV	191	100	Placebo - HRV	0.00	-4.09	1.97

N = number of subjects with available results

% = percentage of subjects with anti-diphtheria concentration ≥ 0.1 IU/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 287 Difference in seroprotection rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-tetanus - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Finland	Placebo	105	100	HRV	167	100	Placebo - HRV	0.00	-3.53	2.25
Italy	Placebo	9	100	HRV	13	100	Placebo - HRV	0.00	-29.91	22.81
Spain	Placebo	90	98.9	HRV	191	99.0	Placebo - HRV	-0.06	-5.04	2.81

N = number of subjects with available results

% = percentage of subjects with anti-tetanus concentration ≥ 0.1 IU/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 288 Difference in seropositivity rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-PT, anti-FHA and anti-PRN - ATP cohort for immunogenicity

								Difference in seropositivity rate			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-PT	**Finland**	Placebo	104	100	HRV	167	100	Placebo - HRV	0.00	-3.56	2.25
	Italy	Placebo	8	100	HRV	13	100	Placebo - HRV	0.00	-32.44	22.81
	Spain	Placebo	90	100	HRV	190	98.4	Placebo - HRV	1.58	-2.54	4.54
Anti-FHA	**Finland**	Placebo	105	100	HRV	167	100	Placebo - HRV	0.00	-3.53	2.25
	Italy	Placebo	9	100	HRV	13	100	Placebo - HRV	0.00	-29.91	22.81
	Spain	Placebo	90	100	HRV	191	100	Placebo - HRV	0.00	-4.09	1.97
Anti-PRN	**Finland**	Placebo	103	99.0	HRV	166	98.8	Placebo - HRV	0.23	-4.17	3.45
	Italy	Placebo	9	100	HRV	13	100	Placebo - HRV	0.00	-29.91	22.81
	Spain	Placebo	90	98.9	HRV	191	96.9	Placebo - HRV	2.03	-3.07	5.78

N = number of subjects with available results

% = percentage of subjects with anti-PT, anti-FHA, anti-PRN concentration ≥ 5 EL.U/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 289 Difference in seroprotection rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-HBs - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Finland	Placebo	105	93.3	HRV	166	97.6	Placebo - HRV	-4.26	-10.95	0.58
France	Placebo	43	97.7	HRV	80	96.3	Placebo - HRV	1.42	-8.60	8.55
Italy	Placebo	8	87.5	HRV	11	100	Placebo - HRV	-12.50	-47.09	15.39
Spain	Placebo	89	94.4	HRV	186	95.7	Placebo - HRV	-1.32	-8.52	3.80

N = number of subjects with available results

% = percentage of subjects with anti-HBs concentration ≥ 10 mIU/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 290 Difference in seroprotection rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-polio type 1, anti-polio type 2 and anti-polio type 3 - ATP cohort for immunogenicity

								Difference in seroprotection rate			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Anti-polio type 1	**Finland**	Placebo	98	86.7	HRV	151	87.4	Placebo - HRV	-0.68	-9.95	7.61
	Italy	Placebo	5	100	HRV	5	100	Placebo - HRV	0.00	-43.45	43.45
	Spain	Placebo	54	94.4	HRV	119	98.3	Placebo - HRV	-3.87	-13.56	1.52
Anti-polio type 2	**Finland**	Placebo	98	61.2	HRV	154	63.0	Placebo - HRV	-1.76	-14.11	10.31
	Italy	Placebo	6	100	HRV	4	100	Placebo - HRV	0.00	-39.03	48.99
	Spain	Placebo	54	83.3	HRV	116	83.6	Placebo - HRV	-0.29	-13.68	10.81
Anti-polio type 3	**Finland**	Placebo	94	87.2	HRV	151	92.1	Placebo - HRV	-4.82	-13.79	2.76
	Italy	Placebo	6	100	HRV	4	75.0	Placebo - HRV	25.00	-20.46	69.94
	Spain	Placebo	50	98.0	HRV	117	97.4	Placebo - HRV	0.56	-8.09	5.66

N = number of subjects with available results

% = percentage of subjects with anti-polio types 1, 2 and 3 titer ≥ 8 ED50

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 291 Difference in seroprotection rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-PRP concentration ≥0.15 mcg/ml - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Finland	Placebo	105	91.4	HRV	167	97.0	Placebo - HRV	-5.58	-12.78	-0.18
Italy	Placebo	9	88.9	HRV	13	92.3	Placebo - HRV	-3.42	-37.42	24.84
Spain	Placebo	90	87.8	HRV	190	84.2	Placebo - HRV	3.57	-5.90	11.58

N = number of subjects with available results

% = percentage of subjects with anti-PRP concentration ≥ 0.15 µg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 292 Difference in seroprotection rates post Dose 2 of childhood vaccinations between placebo and HRV groups, for anti-PRP concentration ≥1 mcg/ml - ATP cohort for immunogenicity

							Difference in seroprotection rate			
									95 % CI	
Country	**Group**	**N**	**%**	**Group**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
Finland	Placebo	105	54.3	HRV	167	57.5	Placebo - HRV	-3.20	-15.25	8.80
Italy	Placebo	9	44.4	HRV	13	69.2	Placebo - HRV	-24.79	-59.23	16.16
Spain	Placebo	90	38.9	HRV	190	45.8	Placebo - HRV	-6.90	-18.82	5.57

N = number of subjects with available results

% = percentage of subjects with anti-PRP concentration ≥ 1 µg/ml

95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 293 Ratio of anti-PSC antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Spain	Placebo	90	6.07	HRV	190	5.25	Placebo / HRV	1.15	0.96	1.39

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 294 Ratio of anti-SBA-MENC antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Spain	Placebo	88	1336.0	HRV	189	1049.9	Placebo / HRV	1.27	0.95	1.70

GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 295 Ratio of anti-diphtheria antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Finland	Placebo	105	0.550	HRV	167	0.569	Placebo / HRV	0.97	0.72	1.30
Italy	Placebo	9	2.876	HRV	13	2.223	Placebo / HRV	1.29	0.68	2.45
Spain	Placebo	90	4.011	HRV	191	3.613	Placebo / HRV	1.11	0.90	1.37

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 296 Ratio of anti-tetanus antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Finland	Placebo	105	1.351	HRV	167	1.206	Placebo / HRV	1.12	0.89	1.41
Italy	Placebo	9	2.765	HRV	13	2.278	Placebo / HRV	1.21	0.56	2.63
Spain	Placebo	90	0.796	HRV	191	0.848	Placebo / HRV	0.94	0.73	1.21

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 297 Ratio of anti-PT, anti-FHA, anti-PRN antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

								GMC ratio			
										95 % CI	
Antibody	Country	Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Anti-PT	Finland	Placebo	104	47.8	HRV	167	50.9	Placebo / HRV	0.94	0.80	1.10
	Italy	Placebo	8	44.0	HRV	13	47.3	Placebo / HRV	0.93	0.40	2.16
	Spain	Placebo	90	28.5	HRV	190	27.0	Placebo / HRV	1.06	0.88	1.27
Anti-FHA	Finland	Placebo	105	173.8	HRV	167	179.0	Placebo / HRV	0.97	0.82	1.15
	Italy	Placebo	9	152.7	HRV	13	241.8	Placebo / HRV	0.63	0.34	1.18
	Spain	Placebo	90	97.0	HRV	191	95.2	Placebo / HRV	1.02	0.84	1.24
Anti-PRN	Finland	Placebo	103	97.9	HRV	166	77.2	Placebo / HRV	1.27	0.95	1.70
	Italy	Placebo	9	168.9	HRV	13	124.0	Placebo / HRV	1.36	0.56	3.31
	Spain	Placebo	90	52.4	HRV	191	49.0	Placebo / HRV	1.07	0.81	1.41

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 298 Ratio of anti- HBs antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Finland	**Placebo**	105	399.7	HRV	166	431.6	Placebo / HRV	0.93	0.63	1.36
France	**Placebo**	43	481.9	HRV	80	401.4	Placebo / HRV	1.20	0.66	2.19
Italy	**Placebo**	8	282.6	HRV	11	711.9	Placebo / HRV	0.40	0.08	1.92
Spain	**Placebo**	89	461.2	HRV	186	334.4	Placebo / HRV	1.38	0.88	2.15

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 299 Ratio of anti-polio antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

								GMC ratio			
										95 % CI	
Antibody	**Country**	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Anti-polio type 1	**Finland**	Placebo	98	37.2	HRV	151	47.3	Placebo / HRV	0.78	0.52	1.19
	Italy	Placebo	5	337.8	HRV	5	415.8	Placebo / HRV	0.81	0.27	2.44
	Spain	Placebo	54	137.4	HRV	119	150.7	Placebo / HRV	0.91	0.56	1.49
Anti-polio type 2	**Finland**	Placebo	98	11.4	HRV	154	11.9	Placebo / HRV	0.96	0.69	1.33
	Italy	Placebo	6	256.0	HRV	4	107.6	Placebo / HRV	2.38	0.52	10.82
	Spain	Placebo	54	40.8	HRV	116	49.6	Placebo / HRV	0.82	0.48	1.41
Anti-polio type 3	**Finland**	Placebo	94	49.5	HRV	151	83.2	Placebo / HRV	0.59	0.38	0.94
	Italy	Placebo	6	304.4	HRV	4	234.8	Placebo / HRV	1.30	0.04	43.36
	Spain	Placebo	50	150.3	HRV	117	299.6	Placebo / HRV	0.50	0.32	0.80

GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 300 Ratio of anti-PRP antibody GMCs, post Dose 2 of childhood vaccinations between placebo and HRV groups - ATP cohort for immunogenicity

							GMC ratio			
									95 % CI	
Country	**Group**	**N**	**GMC**	**Group**	**N**	**GMC**	**Ratio order**	**Value**	**LL**	**UL**
Finland	Placebo	105	1.365	HRV	167	1.671	Placebo / HRV	0.82	0.56	1.19
Italy	Placebo	9	1.905	HRV	13	2.313	Placebo / HRV	0.82	0.13	5.08
Spain	Placebo	90	0.722	HRV	190	0.816	Placebo / HRV	0.88	0.61	1.29

GMC = geometric mean antibody concentration

N = Number of subjects with post-vaccination results available

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 301 Seropositivity rates and GMCs for anti-rotavirus IgA antibodies – Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 20 U/ML				GMC		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Czech Republic	HRV	PRE	195	0	0.0	0.0	1.9	< 20	-	-
		PII(M3-M4)	193	163	84.5	78.6	89.3	148.5	117.1	188.3
	Placebo	PRE	98	1	1.0	0.0	5.6	< 20	-	-
		PII(M3-M4)	100	2	2.0	0.2	7.0	< 20	-	-
Finland	HRV	PRE	186	0	0.0	0.0	2.0	< 20	-	-
		PII(M3-M4)	173	164	94.8	90.4	97.6	411.8	327.9	517.2
	Placebo	PRE	113	1	0.9	0.0	4.8	< 20	-	-
		PII(M3-M4)	109	4	3.7	1.0	9.1	< 20	-	-
France	HRV	PRE	95	0	0.0	0.0	3.8	< 20	-	-
		PII(M3-M4)	88	75	85.2	76.1	91.9	182.4	128.7	258.5
	Placebo	PRE	51	0	0.0	0.0	7.0	< 20	-	-
		PII(M3-M4)	48	7	14.6	6.1	27.8	16.5	11.0	24.9
Germany	HRV	PRE	187	3	1.6	0.3	4.6	< 20	-	-
		PII(M3-M4)	172	141	82.0	75.4	87.4	166.1	128.0	215.6
	Placebo	PRE	96	0	0.0	0.0	3.8	< 20	-	-
		PII(M3-M4)	96	7	7.3	3.0	14.4	< 20	-	-
Italy	HRV	PRE	15	0	0.0	0.0	21.8	< 20	-	-
		PII(M3-M4)	15	14	93.3	68.1	99.8	220.8	98.9	493.0
	Placebo	PRE	10	0	0.0	0.0	30.8	< 20	-	-
		PII(M3-M4)	10	1	10.0	0.3	44.5	< 20	-	-
Spain	HRV	PRE	224	16	7.1	4.1	11.3	< 20	-	-
		PII(M3-M4)	213	185	86.9	81.6	91.1	160.4	129.1	199.4
		PII(M5)	212	178	84.0	78.3	88.6	117.8	95.9	144.8
	Placebo	PRE	111	8	7.2	3.2	13.7	< 20	-	-
		PII(M3-M4)	110	24	21.8	14.5	30.7	22.6	16.4	31.1
		PII(M5)	110	26	23.6	16.1	32.7	21.9	16.3	29.4
All	HRV	PRE	902	19	2.1	1.3	3.3	< 20	-	-
		PII(M3-M4)	854	742	86.9	84.4	89.1	195.8	175.0	219.1
		PII(M5)	212	178	84.0	78.3	88.6	117.8	95.9	144.8
	Placebo	PRE	479	10	2.1	1.0	3.8	< 20	-	-
		PII(M3-M4)	473	45	9.5	7.0	12.5	< 20	-	-
		PII(M5)	110	26	23.6	16.1	32.7	21.9	16.3	29.4

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Supplement 302 Anti-rotavirus IgA antibody GMC calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at Visit 3 (4) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				GMC		
					95% CI	
Country	Group	Timing	N	value	LL	UL
Czech Republic	HRV	PII(M3-M4)	163	244.0	199.2	298.9
	Placebo	PRE	1	40.0	-	-
		PII(M3-M4)	2	840.9	78.9	8961.3
Finland	HRV	PII(M3-M4)	164	505.0	414.9	614.8
	Placebo	PRE	1	61.0	-	-
		PII(M3-M4)	4	106.6	7.7	1482.3
France	HRV	PII(M3-M4)	75	301.7	228.9	397.8
	Placebo	PII(M3-M4)	7	311.7	50.4	1928.0
Germany	HRV	PRE	3	122.7	58.6	257.2
		PII(M3-M4)	141	308.1	250.8	378.6
	Placebo	PII(M3-M4)	7	1024.6	321.7	3263.1
Italy	HRV	PII(M3-M4)	14	275.4	136.6	555.5
	Placebo	PII(M3-M4)	1	57.0	-	-
Spain	HRV	PRE	16	496.9	240.5	1026.8
		PII(M3-M4)	185	244.1	202.8	293.9
		PII(M5)	178	188.8	158.8	224.4
	Placebo	PRE	8	1016.1	639.5	1614.5
		PII(M3-M4)	24	419.6	224.1	785.7
		PII(M5)	26	276.2	162.4	469.7
All	HRV	PRE	19	398.5	207.6	764.8
		PII(M3-M4)	742	306.8	279.4	336.8
		PII(M5)	178	188.8	158.8	224.4
	Placebo	PRE	10	555.0	208.4	1477.7
		PII(M3-M4)	45	402.1	249.9	647.0
		PII(M5)	26	276.2	162.4	469.7

N = number of subjects who are seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Supplement 303 Seropositivity rates and GMCs for anti-rotavirus IgA antibodies, by feeding criteria – pooled countries - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 20 U/ML				GMC		
						95% CI			95% CI	
Breast feeding	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
For at least one dose	**HRV**	**PRE**	638	9	1.4	0.6	2.7	< 20	-	-
		PII(M3-M4)	615	526	85.5	82.5	88.2	183.2	160.0	209.6
		PII(M5)	144	120	83.3	76.2	89.0	120.6	93.8	155.0
	Placebo	**PRE**	358	6	1.7	0.6	3.6	< 20	-	-
		PII(M3-M4)	359	26	7.2	4.8	10.4	< 20	-	-
		PII(M5)	76	12	15.8	8.4	26.0	< 20	-	-
At none of the doses	**HRV**	**PRE**	264	10	3.8	1.8	6.9	< 20	-	-
		PII(M3-M4)	239	216	90.4	85.9	93.8	232.6	190.2	284.5
		PII(M5)	68	58	85.3	74.6	92.7	112.2	77.6	162.2
	Placebo	**PRE**	121	4	3.3	0.9	8.2	< 20	-	-
		PII(M3-M4)	114	19	16.7	10.3	24.8	< 20	-	-
		PII(M5)	34	14	41.2	24.6	59.3	34.5	18.6	63.7

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Supplement 304 Anti-rotavirus IgA antibody GMC calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at Visit 3 (4), by feeding criteria – pooled countries - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				GMC		
					95% CI	
Breast feeding	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
For at least one dose	**HRV**	**PRE**	9	618.2	261.6	1461.2
		PII(M3-M4)	526	299.6	267.8	335.1
		PII(M5)	120	198.5	161.6	243.7
	Placebo	**PRE**	6	378.2	71.1	2013.1
		PII(M3-M4)	26	432.5	236.7	790.1
		PII(M5)	12	398.5	204.8	775.2
At none of the doses	**HRV**	**PRE**	10	268.3	93.3	771.7
		PII(M3-M4)	216	325.2	274.5	385.1
		PII(M5)	58	170.2	123.0	235.4
	Placebo	**PRE**	4	986.6	271.9	3579.6
		PII(M3-M4)	19	363.9	157.5	840.7
		PII(M5)	14	201.8	86.3	471.8

N = number of subjects who are seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
PII(M5) = blood sample taken three months after Dose 2 of HRV vaccine or placebo (Visit 4)

Supplement 305 Seropositivity rates and GMTs for anti-SBA-MENC antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 8 1/DIL.				≥ 128 1/DIL.				GMT		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Spain	HRV	PII(M3-M4)	218	218	100	98.3	100	212	97.2	94.1	99.0	1039.3	889.6	1214.0
	Placebo	PII(M3-M4)	108	108	100	96.6	100	104	96.3	90.8	99.0	1266.8	1030.9	1556.6

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 306 Seropositivity rates and GMTs for anti-SBA-MENC antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 8 1/DIL.				≥ 128 1/DIL.				GMT		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Spain	HRV	PIII(M3-M5)	215	215	100	98.3	100	212	98.6	96.0	99.7	1439.9	1241.6	1669.9
	Placebo	PIII(M3-M5)	112	112	100	96.8	100	112	100	96.8	100	1671.1	1351.5	2066.3

Seroprotection = SBA-MENC antibody titer ≥ 128 1/DIL.
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4)

Supplement 307 Seropositivity rates and GMCs for anti-PSC antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.3 µg/ml				≥ 2 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Spain	HRV	PII(M3-M4)	221	221	100	98.3	100	204	92.3	88.0	95.5	5.46	4.93	6.05
	Placebo	PII(M3-M4)	112	112	100	96.8	100	104	92.9	86.4	96.9	5.90	5.17	6.75

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 308 Seropositivity rates and GMCs for anti-PSC antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.3 µg/ml				≥ 2 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Country	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Spain	**HRV**	**PIII(M3-M5)**	219	219	100	98.3	100	214	97.7	94.8	99.3	7.81	7.02	8.69
	Placebo	**PIII(M3-M5)**	113	113	100	96.8	100	109	96.5	91.2	99.0	8.35	7.29	9.55

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4)

Supplement 309 Seropositivity rates and GMCs for antibodies to *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 0.05 µg/ml				≥ 0.2 µg/ml				GMC		
							95% CI				95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
PNEUMONIA-4	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	93	100	96.1	3.9	2.31	1.96	2.72
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	49	100	92.7	7.3	2.45	2.07	2.90
	Germany	HRV	PIII(M3-M5)	177	177	100	97.9	100	177	100	97.9	2.1	3.16	2.80	3.57
		Placebo	PIII(M3-M5)	98	98	100	96.3	100	98	100	96.3	3.7	3.01	2.51	3.60
PNEUMONIA-6B	France	HRV	PIII(M3-M5)	93	90	96.8	90.9	99.3	78	83.9	74.8	3.9	0.76	0.58	1.00
		Placebo	PIII(M3-M5)	49	48	98.0	89.1	99.9	44	89.8	77.8	7.3	0.72	0.52	1.00
	Germany	HRV	PIII(M3-M5)	177	158	89.3	83.7	93.4	125	70.6	63.3	2.1	0.53	0.41	0.69
		Placebo	PIII(M3-M5)	98	91	92.9	85.8	97.1	69	70.4	60.3	3.7	0.51	0.37	0.70
PNEUMONIA-9V	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	93	100	96.1	3.9	2.36	2.04	2.73
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	49	100	92.7	7.3	2.47	2.04	2.99
	Germany	HRV	PIII(M3-M5)	177	176	99.4	96.9	100	175	98.9	96.0	2.1	2.87	2.49	3.29
		Placebo	PIII(M3-M5)	98	98	100	96.3	100	98	100	96.3	3.7	2.71	2.23	3.28
PNEUMONIA-14	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	93	100	96.1	3.9	4.63	3.78	5.68
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	49	100	92.7	7.3	5.26	4.24	6.53
	Germany	HRV	PIII(M3-M5)	178	178	100	97.9	100	177	99.4	96.9	2.1	4.56	3.92	5.31
		Placebo	PIII(M3-M5)	98	98	100	96.3	100	97	99.0	94.4	3.7	4.15	3.26	5.27
PNEUMONIA-18C	France	HRV	PIII(M3-M5)	93	91	97.8	92.4	99.7	90	96.8	90.9	3.9	2.49	1.97	3.14
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	49	100	92.7	7.3	2.64	2.08	3.36
	Germany	HRV	PIII(M3-M5)	178	178	100	97.9	100	177	99.4	96.9	2.1	3.32	2.84	3.89
		Placebo	PIII(M3-M5)	98	98	100	96.3	100	95	96.9	91.3	3.7	3.13	2.50	3.92
PNEUMONIA-19F	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	91	97.8	92.4	3.9	2.74	2.25	3.33
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	48	98.0	89.1	7.3	2.60	1.96	3.45
	Germany	HRV	PIII(M3-M5)	177	177	100	97.9	100	175	98.9	96.0	2.1	3.53	3.03	4.12
		Placebo	PIII(M3-M5)	98	98	100	96.3	100	97	99.0	94.4	3.7	3.28	2.69	4.00

					≥ 0.05 µg/ml				≥ 0.2 µg/ml				GMC		
							95% CI				95% CI			95% CI	
Antibody	**Country**	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
PNEUMONIA-23F	**France**	**HRV**	**PIII(M3-M5)**	93	91	97.8	92.4	99.7	84	90.3	82.4	3.9	1.14	0.87	1.48
		Placebo	**PIII(M3-M5)**	49	49	100	92.7	100	47	95.9	86.0	7.3	1.42	1.08	1.87
	Germany	**HRV**	**PIII(M3-M5)**	178	169	94.9	90.6	97.7	157	88.2	82.5	2.1	1.30	1.03	1.64
		Placebo	**PIII(M3-M5)**	98	93	94.9	88.5	98.3	83	84.7	76.0	3.7	1.23	0.87	1.74

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 3)

Supplement 310 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 0.1 IU/ML				GMC		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	Finland	HRV	PII(M3-M4)	179	164	91.6	86.6	95.2	0.585	0.487	0.703
		Placebo	PII(M3-M4)	110	103	93.6	87.3	97.4	0.554	0.445	0.690
	Italy	HRV	PII(M3-M4)	15	15	100	78.2	100	2.086	1.353	3.217
		Placebo	PII(M3-M4)	10	10	100	69.2	100	2.943	2.085	4.153
	Spain	HRV	PII(M3-M4)	222	222	100	98.4	100	3.546	3.179	3.956
		Placebo	PII(M3-M4)	112	112	100	96.8	100	3.920	3.317	4.632
Anti-tetanus	Finland	HRV	PII(M3-M4)	179	179	100	98.0	100	1.214	1.058	1.393
		Placebo	PII(M3-M4)	110	110	100	96.7	100	1.353	1.140	1.605
	Italy	HRV	PII(M3-M4)	15	15	100	78.2	100	2.412	1.568	3.711
		Placebo	PII(M3-M4)	10	10	100	69.2	100	2.895	1.543	5.430
	Spain	HRV	PII(M3-M4)	222	220	99.1	96.8	99.9	0.860	0.756	0.979
		Placebo	PII(M3-M4)	112	111	99.1	95.1	100	0.803	0.660	0.976

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 311 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 0.1 IU/ML				GMC		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-diphtheria	Czech Republic	HRV	PIII(M3-M5)	195	195	100	98.1	100	2.272	2.051	2.517
		Placebo	PIII(M3-M5)	99	99	100	96.3	100	2.658	2.282	3.096
	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	1.096	0.917	1.309
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	1.169	0.894	1.528
	Germany	HRV	PIII(M3-M5)	177	170	96.0	92.0	98.4	1.480	1.233	1.777
		Placebo	PIII(M3-M5)	98	97	99.0	94.4	100	1.468	1.167	1.847
	Spain	HRV	PIII(M3-M5)	220	220	100	98.3	100	6.472	5.950	7.040
		Placebo	PIII(M3-M5)	112	112	100	96.8	100	6.789	5.945	7.753
Anti-tetanus	Czech Republic	HRV	PIII(M3-M5)	195	195	100	98.1	100	1.915	1.699	2.159
		Placebo	PIII(M3-M5)	100	100	100	96.4	100	1.915	1.618	2.267
	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	1.312	1.109	1.550
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	1.345	1.100	1.645
	Germany	HRV	PIII(M3-M5)	177	173	97.7	94.3	99.4	1.130	0.959	1.330
		Placebo	PIII(M3-M5)	98	98	100	96.3	100	1.181	0.967	1.441
	Spain	HRV	PIII(M3-M5)	220	219	99.5	97.5	100	1.692	1.509	1.897
		Placebo	PIII(M3-M5)	111	111	100	96.7	100	1.683	1.448	1.956

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4 for Spain, Visit 3 for other countries)

Supplement 312 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 5 EL.U/ML				GMC		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Finland	HRV	PII(M3-M4)	179	179	100	98.0	100	50.4	45.7	55.5
		Placebo	PII(M3-M4)	109	109	100	96.7	100	48.0	42.3	54.3
	Italy	HRV	PII(M3-M4)	15	15	100	78.2	100	49.9	28.9	86.3
		Placebo	PII(M3-M4)	9	9	100	66.4	100	42.3	27.9	64.2
	Spain	HRV	PII(M3-M4)	221	217	98.2	95.4	99.5	27.1	24.5	30.1
		Placebo	PII(M3-M4)	112	111	99.1	95.1	100	28.2	25.0	31.8
Anti-FHA	Finland	HRV	PII(M3-M4)	179	179	100	98.0	100	180.4	162.1	200.7
		Placebo	PII(M3-M4)	110	110	100	96.7	100	173.5	153.2	196.5
	Italy	HRV	PII(M3-M4)	15	15	100	78.2	100	229.4	154.0	341.6
		Placebo	PII(M3-M4)	10	10	100	69.2	100	149.5	102.4	218.2
	Spain	HRV	PII(M3-M4)	222	222	100	98.4	100	95.7	86.3	106.1
		Placebo	PII(M3-M4)	112	112	100	96.8	100	99.7	85.4	116.3
Anti-PRN	Finland	HRV	PII(M3-M4)	178	176	98.9	96.0	99.9	79.4	66.5	94.7
		Placebo	PII(M3-M4)	108	107	99.1	94.9	100	95.2	76.2	118.8
	Italy	HRV	PII(M3-M4)	15	15	100	78.2	100	121.2	65.2	225.5
		Placebo	PII(M3-M4)	10	10	100	69.2	100	163.1	117.6	226.1
	Spain	HRV	PII(M3-M4)	222	215	96.8	93.6	98.7	50.2	43.2	58.3
		Placebo	PII(M3-M4)	112	110	98.2	93.7	99.8	51.8	41.7	64.5

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 313 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 5 EL.U/ML				GMC		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	Czech Republic	HRV	PIII(M3-M5)	194	193	99.5	97.2	100	55.8	51.0	61.0
		Placebo	PIII(M3-M5)	100	100	100	96.4	100	53.9	47.4	61.4
	France	HRV	PIII(M3-M5)	93	93	100	96.1	100	42.2	37.6	47.3
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	46.4	39.9	54.0
	Germany	HRV	PIII(M3-M5)	175	161	92.0	86.9	95.6	31.2	26.9	36.2
		Placebo	PIII(M3-M5)	96	91	94.8	88.3	98.3	30.5	25.5	36.4
	Spain	HRV	PIII(M3-M5)	220	219	99.5	97.5	100	43.0	39.5	46.9
		Placebo	PIII(M3-M5)	112	112	100	96.8	100	45.5	40.9	50.5
Anti-FHA	Czech Republic	HRV	PIII(M3-M5)	195	195	100	98.1	100	216.3	197.2	237.2
		Placebo	PIII(M3-M5)	100	100	100	96.4	100	217.5	192.1	246.3
	France	HRV	PIII(M3-M5)	92	92	100	96.1	100	169.3	148.2	193.4
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	179.5	153.2	210.3
	Germany	HRV	PIII(M3-M5)	177	174	98.3	95.1	99.6	120.4	100.1	144.9
		Placebo	PIII(M3-M5)	98	96	98.0	92.8	99.8	111.6	87.3	142.8
	Spain	HRV	PIII(M3-M5)	220	220	100	98.3	100	161.3	147.3	176.6
		Placebo	PIII(M3-M5)	112	112	100	96.8	100	164.1	144.3	186.7
Anti-PRN	Czech Republic	HRV	PIII(M3-M5)	195	195	100	98.1	100	111.5	99.6	124.8
		Placebo	PIII(M3-M5)	100	100	100	96.4	100	111.2	94.5	130.8
	France	HRV	PIII(M3-M5)	92	92	100	96.1	100	100.5	84.5	119.5
		Placebo	PIII(M3-M5)	49	49	100	92.7	100	105.8	80.9	138.4
	Germany	HRV	PIII(M3-M5)	177	169	95.5	91.3	98.0	78.7	65.1	95.2
		Placebo	PIII(M3-M5)	98	95	96.9	91.3	99.4	78.7	60.8	102.0
	Spain	HRV	PIII(M3-M5)	220	220	100	98.3	100	105.1	94.7	116.6
		Placebo	PIII(M3-M5)	112	112	100	96.8	100	110.5	94.7	129.0

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4 for Spain, Visit 3 for other countries)

Supplement 314 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Finland	HRV	PII(M3-M4)	178	174	97.8	94.3	99.4	431.6	349.7	532.6
	Placebo	PII(M3-M4)	110	103	93.6	87.3	97.4	405.2	293.8	558.8
France	HRV	PII(M3-M4)	89	86	96.6	90.5	99.3	431.0	309.4	600.2
	Placebo	PII(M3-M4)	49	48	98.0	89.1	99.9	478.3	303.8	753.0
Italy	HRV	PII(M3-M4)	13	13	100	75.3	100	716.5	325.9	1575.5
	Placebo	PII(M3-M4)	9	8	88.9	51.8	99.7	320.0	82.8	1236.0
Spain	HRV	PII(M3-M4)	217	206	94.9	91.1	97.4	340.2	269.7	429.2
	Placebo	PII(M3-M4)	111	105	94.6	88.6	98.0	453.6	323.5	635.9

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 315 Seroprotection rates and GMCs for anti-HBs antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Czech Republic	HRV	PIII(M3-M5)	194	190	97.9	94.8	99.4	413.0	335.0	509.1
	Placebo	PIII(M3-M5)	100	98	98.0	93.0	99.8	348.8	263.3	462.0
Germany	HRV	PIII(M3-M5)	174	139	79.9	73.2	85.6	158.4	115.8	216.6
	Placebo	PIII(M3-M5)	96	79	82.3	73.2	89.3	150.3	101.0	223.7
Spain	HRV	PIII(M3-M5)	219	214	97.7	94.8	99.3	835.2	685.0	1018.4
	Placebo	PIII(M3-M5)	111	105	94.6	88.6	98.0	865.1	616.6	1213.7

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4 for Spain, Visit 3 for other countries)

Supplement 316 Seroprotection rates and GMTs for anti-polio type 1, anti-polio type 2 and anti-polio type 3 antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 8 ED50				GMT		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-polio type 1	Finland	HRV	PII(M3-M4)	161	139	86.3	80.0	91.2	44.5	34.4	57.6
		Placebo	PII(M3-M4)	103	89	86.4	78.2	92.4	37.3	27.2	51.2
	Italy	HRV	PII(M3-M4)	6	6	100	54.1	100	456.1	241.2	862.3
		Placebo	PII(M3-M4)	5	5	100	47.8	100	337.8	115.7	986.2
	Spain	HRV	PII(M3-M4)	134	132	98.5	94.7	99.8	146.8	114.1	189.0
		Placebo	PII(M3-M4)	67	64	95.5	87.5	99.1	143.4	98.2	209.6
Anti-polio type 2	Finland	HRV	PII(M3-M4)	164	101	61.6	53.7	69.1	11.5	9.4	14.1
		Placebo	PII(M3-M4)	102	62	60.8	50.6	70.3	11.9	9.3	15.3
	Italy	HRV	PII(M3-M4)	5	5	100	47.8	100	181.0	20.2	1624.2
		Placebo	PII(M3-M4)	6	6	100	54.1	100	256.0	153.1	428.2
	Spain	HRV	PII(M3-M4)	133	113	85.0	77.7	90.6	54.1	40.4	72.4
		Placebo	PII(M3-M4)	69	55	79.7	68.3	88.4	44.8	28.9	69.3
Anti-polio type 3	Finland	HRV	PII(M3-M4)	162	149	92.0	86.7	95.7	76.7	58.2	101.1
		Placebo	PII(M3-M4)	99	86	86.9	78.6	92.8	51.8	35.7	75.1
	Italy	HRV	PII(M3-M4)	5	4	80.0	28.4	99.5	388.0	11.2	13383.7
		Placebo	PII(M3-M4)	6	6	100	54.1	100	304.4	44.0	2107.4
	Spain	HRV	PII(M3-M4)	132	129	97.7	93.5	99.5	306.9	243.6	386.7
		Placebo	PII(M3-M4)	63	62	98.4	91.5	100	186.2	129.5	267.7

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 317 Seroprotection rates and GMTs for anti-polio type 1, anti-polio type 2 and anti-polio type 3 antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

					≥ 8 ED50				GMT		
							95% CI			95% CI	
Antibody	Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-polio type 1	Czech Republic	HRV	PIII(M3-M5)	130	130	100	97.2	100	457.8	357.9	585.6
		Placebo	PIII(M3-M5)	71	71	100	94.9	100	351.7	260.1	475.6
	France	HRV	PIII(M3-M5)	51	51	100	93.0	100	100.2	67.7	148.2
		Placebo	PIII(M3-M5)	34	33	97.1	84.7	99.9	132.2	75.1	232.4
	Germany	HRV	PIII(M3-M5)	122	113	92.6	86.5	96.6	126.8	89.7	179.1
		Placebo	PIII(M3-M5)	66	61	92.4	83.2	97.5	96.9	62.6	150.0
	Spain	HRV	PIII(M3-M5)	144	144	100	97.5	100	653.0	532.6	800.6
		Placebo	PIII(M3-M5)	71	71	100	94.9	100	601.2	453.8	796.6
Anti-polio type 2	Czech Republic	HRV	PIII(M3-M5)	132	132	100	97.2	100	391.8	303.7	505.3
		Placebo	PIII(M3-M5)	65	63	96.9	89.3	99.6	277.4	179.3	429.2
	France	HRV	PIII(M3-M5)	51	48	94.1	83.8	98.8	51.4	34.0	77.7
		Placebo	PIII(M3-M5)	34	31	91.2	76.3	98.1	42.6	24.3	74.5
	Germany	HRV	PIII(M3-M5)	125	106	84.8	77.3	90.6	71.1	49.9	101.2
		Placebo	PIII(M3-M5)	69	58	84.1	73.3	91.8	57.9	36.9	90.7
	Spain	HRV	PIII(M3-M5)	138	137	99.3	96.0	100	414.8	327.3	525.8
		Placebo	PIII(M3-M5)	71	71	100	94.9	100	296.4	214.1	410.3
Anti-polio type 3	Czech Republic	HRV	PIII(M3-M5)	120	120	100	97.0	100	1169.5	907.6	1507.1
		Placebo	PIII(M3-M5)	69	68	98.6	92.2	100	841.9	581.4	1219.1
	France	HRV	PIII(M3-M5)	50	50	100	92.9	100	235.9	145.9	381.4
		Placebo	PIII(M3-M5)	34	34	100	89.7	100	192.6	109.3	339.7
	Germany	HRV	PIII(M3-M5)	123	110	89.4	82.6	94.3	233.9	155.7	351.4
		Placebo	PIII(M3-M5)	66	59	89.4	79.4	95.6	130.0	75.4	224.0
	Spain	HRV	PIII(M3-M5)	142	139	97.9	94.0	99.6	1145.6	894.3	1467.6
		Placebo	PIII(M3-M5)	65	64	98.5	91.7	100	827.2	567.7	1205.3

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4 for Spain, Visit 3 for other countries)

Supplement 318 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 2 of childhood vaccination (Visit 3) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.15 µg/ml				≥ 1 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Finland	HRV	PII(M3-M4)	179	174	97.2	93.6	99.1	107	59.8	52.2	67.0	1.827	1.453	2.298
	Placebo	PII(M3-M4)	110	101	91.8	85.0	96.2	59	53.6	43.9	63.2	1.375	1.019	1.854
Italy	HRV	PII(M3-M4)	15	13	86.7	59.5	98.3	10	66.7	38.4	88.2	1.924	0.652	5.676
	Placebo	PII(M3-M4)	10	9	90.0	55.5	99.7	5	50.0	18.7	81.3	2.298	0.486	10.861
Spain	HRV	PII(M3-M4)	221	190	86.0	80.7	90.3	106	48.0	41.2	54.8	0.937	0.762	1.153
	Placebo	PII(M3-M4)	112	96	85.7	77.8	91.6	47	42.0	32.7	51.7	0.775	0.579	1.038

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3-M4) = post Dose 2 of childhood vaccination (Visit 3)

Supplement 319 Seroprotection rates and GMCs for anti-PRP antibodies post Dose 3 of childhood vaccination - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.15 µg/ml				≥ 1 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
Czech Republic	HRV	PIII(M3-M5)	195	192	98.5	95.6	99.7	149	76.4	69.8	82.2	2.954	2.436	3.581
	Placebo	PIII(M3-M5)	100	100	100	96.4	100	71	71.0	61.1	79.6	2.276	1.771	2.924
France	HRV	PIII(M3-M5)	90	85	94.4	87.5	98.2	54	60.0	49.1	70.2	1.369	1.018	1.839
	Placebo	PIII(M3-M5)	49	48	98.0	89.1	99.9	29	59.2	44.2	73.0	1.363	0.966	1.924
Germany	HRV	PIII(M3-M5)	176	153	86.9	81.0	91.5	105	59.7	52.0	67.0	1.386	1.078	1.782
	Placebo	PIII(M3-M5)	97	81	83.5	74.6	90.3	60	61.9	51.4	71.5	1.194	0.848	1.682
Spain	HRV	PIII(M3-M5)	219	214	97.7	94.8	99.3	178	81.3	75.5	86.2	3.176	2.623	3.846
	Placebo	PIII(M3-M5)	113	106	93.8	87.7	97.5	89	78.8	70.1	85.9	2.706	2.022	3.620

N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII(M3-M5) = post Dose 3 of childhood vaccination (Visit 4 for Spain, Visit 3 for other countries)

Supplement 320 Number and percentage of subjects who received HRV/placebo dose(s) – Czech Republic – Total vaccinated cohort

	HRV N = 199		Placebo N = 100		Total N = 299	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	1	0.5	0	0.0	1	0.3
2	198	99.5	100	100	298	99.7
At least one	199	100	100	100	299	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV/Placebo

Supplement 321 Number and percentage of subjects who received HRV/placebo dose(s) – Finland – Total vaccinated cohort

	HRV N = 1918		Placebo N = 972		Total N = 2890	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	18	0.9	7	0.7	25	0.9
2	1900	99.1	965	99.3	2865	99.1
At least one	1918	100	972	100	2890	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV/Placebo

Supplement 322 Number and percentage of subjects who received HRV/placebo dose(s) – France – Total vaccinated cohort

	HRV N = 95		Placebo N = 51		Total N = 146	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	0	0.0	0	0.0	0	0.0
2	95	100	51	100	146	100
At least one	95	100	51	100	146	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV/Placebo

Supplement 323 Number and percentage of subjects who received HRV/placebo dose(s) – Germany – Total vaccinated cohort

	HRV N = 190		Placebo N = 99		Total N = 289	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	3	1.6	0	0.0	3	1.0
2	187	98.4	99	100	286	99.0
At least one	190	100	99	100	289	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV/Placebo

Supplement 324 Number and percentage of subjects who received HRV/placebo dose(s) – Italy – Total vaccinated cohort

	HRV N = 15		Placebo N = 10		Total N = 25	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	0	0.0	0	0.0	0	0.0
2	15	100	10	100	25	100
At least one	15	100	10	100	25	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV/Placebo

Supplement 325 Number and percentage of subjects who received HRV/placebo dose(s) – Spain – Total vaccinated cohort

	HRV N = 229		Placebo N = 116		Total N = 345	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	3	1.3	3	2.6	6	1.7
2	226	98.7	113	97.4	339	98.3
At least one	229	100	116	100	345	100

N = number of subjects in each group or in total (sum of both groups)
n/% = number/percentage of subjects who received the specified number of doses of HRV/Placebo

Supplement 326 Compliance in returning symptom sheets – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	**HRV**	914	909	99.5
	Placebo	490	488	99.6
2	**HRV**	905	899	99.3
	Placebo	486	485	99.8
Total doses	**HRV**	1819	1808	99.4
	Placebo	976	973	99.7

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 327 Compliance in returning symptom sheets – Czech Republic – Total vaccinated cohort

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	**HRV**	199	199	100
	Placebo	100	100	100
2	**HRV**	198	198	100
	Placebo	100	100	100
Total	**HRV**	397	397	100
	Placebo	200	200	100

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 328 Compliance in returning symptom sheets – Finland – Total vaccinated cohort for the reactogenicity and immunogenicity subset

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	**HRV**	186	185	99.5
	Placebo	114	114	100
2	**HRV**	184	184	100
	Placebo	113	113	100
Total	**HRV**	370	369	99.7
	Placebo	227	227	100

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 329 Compliance in returning symptom sheets – France – Total Vaccinated cohort

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	**HRV**	95	95	100
	Placebo	51	51	100
2	**HRV**	95	95	100
	Placebo	51	50	98.0
Total	**HRV**	190	190	100
	Placebo	102	101	99.0

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 330 Compliance in returning symptom sheets – Germany – Total vaccinated cohort

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	**HRV**	190	188	98.9
	Placebo	99	99	100
2	**HRV**	187	182	97.3
	Placebo	99	99	100
Total	**HRV**	377	370	98.1
	Placebo	198	198	100

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 331 Compliance in returning symptom sheets – Italy – Total vaccinated cohort

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	HRV	15	15	100
	Placebo	10	10	100
2	HRV	15	15	100
	Placebo	10	10	100
Total	HRV	30	30	100
	Placebo	20	20	100

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 332 Compliance in returning symptom sheets – Spain – Total vaccinated cohort

Dose number	Group	Number of doses administered	Number of general SS returned	Compliance % of general SS
1	HRV	229	227	99.1
	Placebo	116	114	98.3
2	HRV	226	225	99.6
	Placebo	113	113	100
Total	HRV	455	452	99.3
	Placebo	229	227	99.1

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of HRV/Placebo doses with symptom sheet returned / number of doses administered) X 100

Supplement 333 Percentage of doses and of subjects with grade 3 symptoms (solicited or unsolicited) reported during the 8 days (Day 0 – Day 7) post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	**HRV**	914	45	4.9	3.6	6.5
	Placebo	490	31	6.3	4.3	8.9
Dose 2	**HRV**	905	40	4.4	3.2	6.0
	Placebo	486	28	5.8	3.9	8.2
Overall/dose	**HRV**	1819	85	4.7	3.7	5.7
	Placebo	976	59	6.0	4.6	7.7
Overall/subject	**HRV**	914	79	8.6	6.9	10.7
	Placebo	490	53	10.8	8.2	13.9

For each dose: N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting at least one grade 3 symptom for the considered dose, during the 8 days follow-up period

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by at least one grade 3 symptom, during the 8 days follow-up period

For overall/subject: N= number of subjects having received at least one dose of HRV/Placebo
n%= number/percentage of subjects reporting at least one grade 3 symptom, during any of the 8 days follow-up periods

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 334 Percentage of doses and of subjects with symptoms (solicited or unsolicited) assessed as causally related to vaccination, reported during the 8 days (Day 0 – Day 7) post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV	914	402	44.0	40.7	47.3
	Placebo	490	226	46.1	41.6	50.7
Dose 2	HRV	905	361	39.9	36.7	43.2
	Placebo	486	202	41.6	37.1	46.1
Overall/dose	HRV	1819	763	41.9	39.7	44.3
	Placebo	976	428	43.9	40.7	47.0
Overall/subject	HRV	914	528	57.8	54.5	61.0
	Placebo	490	296	60.4	55.9	64.8

For each dose: N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting at least one symptom assessed as causally related to vaccination for the considered dose, during the 8 days follow-up period

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by at least one symptom assessed as causally related to vaccination, during the 8 days follow-up period

For overall/subject: N= number of subjects having received at least one dose of HRV/Placebo
n%= number/percentage of subjects reporting at least one symptom assessed as causally related to vaccination, during any of the 8 days follow-up periods

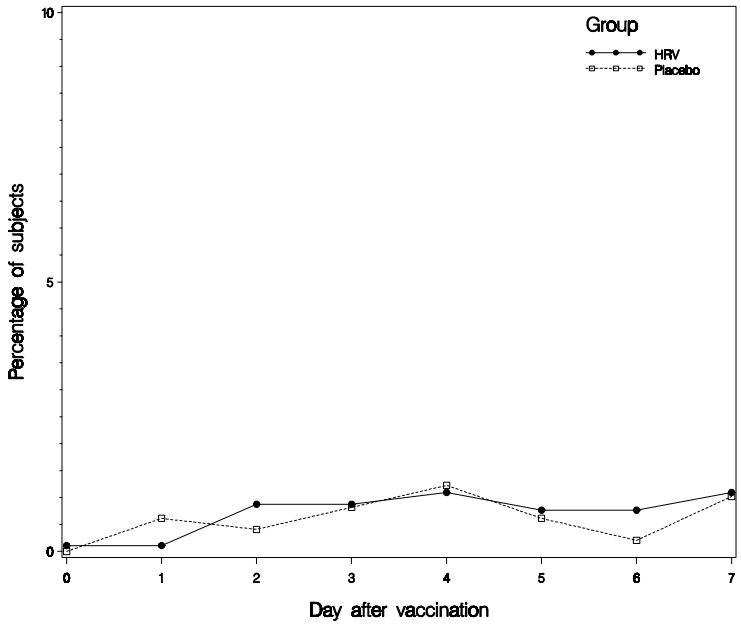
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 335 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	N	%	LL	UL	N	n	%	LL	UL
Overall/dose											
Cough/Runny nose	Total	1819	455	25.0	23.0	27.1	976	266	27.3	24.5	30.2
	Grade 3	1819	17	0.9	0.5	1.5	976	3	0.3	0.1	0.9
	Related	1819	111	6.1	5.0	7.3	976	63	6.5	5.0	8.2
Diarrhea	Total	1819	39	2.1	1.5	2.9	976	20	2.0	1.3	3.1
	Grade 3	1819	9	0.5	0.2	0.9	976	10	1.0	0.5	1.9
	Related	1819	24	1.3	0.8	2.0	976	15	1.5	0.9	2.5
Fever	Total	1819	410	22.5	20.6	24.5	976	233	23.9	21.2	26.7
	Grade 3	1819	2	0.1	0.0	0.4	976	4	0.4	0.1	1.0
	Related	1819	297	16.3	14.7	18.1	976	162	16.6	14.3	19.1
Irritability/Fussiness	Total	1819	850	46.7	44.4	49.1	976	465	47.6	44.5	50.8
	Grade 3	1819	44	2.4	1.8	3.2	976	26	2.7	1.7	3.9
	Related	1819	537	29.5	27.4	31.7	976	294	30.1	27.3	33.1
Loss of appetite	Total	1819	405	22.3	20.4	24.2	976	202	20.7	18.2	23.4
	Grade 3	1819	10	0.5	0.3	1.0	976	2	0.2	0.0	0.7
	Related	1819	244	13.4	11.9	15.1	976	128	13.1	11.1	15.4
Vomiting	Total	1819	154	8.5	7.2	9.8	976	98	10.0	8.2	12.1
	Grade 3	1819	19	1.0	0.6	1.6	976	13	1.3	0.7	2.3
	Related	1819	62	3.4	2.6	4.3	976	47	4.8	3.6	6.4
Overall/subject											
Cough/Runny nose	Total	914	366	40.0	36.8	43.3	490	205	41.8	37.4	46.3
	Grade 3	914	16	1.8	1.0	2.8	490	3	0.6	0.1	1.8
	Related	914	99	10.8	8.9	13.0	490	52	10.6	8.0	13.7
Diarrhea	Total	914	38	4.2	3.0	5.7	490	20	4.1	2.5	6.2
	Grade 3	914	9	1.0	0.5	1.9	490	10	2.0	1.0	3.7
	Related	914	24	2.6	1.7	3.9	490	15	3.1	1.7	5.0
Fever	Total	914	310	33.9	30.8	37.1	490	192	39.2	34.8	43.7
	Grade 3	914	2	0.2	0.0	0.8	490	4	0.8	0.2	2.1
	Related	914	234	25.6	22.8	28.6	490	137	28.0	24.0	32.2
Irritability/Fussiness	Total	914	567	62.0	58.8	65.2	490	308	62.9	58.4	67.1
	Grade 3	914	40	4.4	3.1	5.9	490	25	5.1	3.3	7.4
	Related	914	395	43.2	40.0	46.5	490	218	44.5	40.0	49.0
Loss of appetite	Total	914	310	33.9	30.8	37.1	490	161	32.9	28.7	37.2
	Grade 3	914	9	1.0	0.5	1.9	490	2	0.4	0.0	1.5
	Related	914	202	22.1	19.4	24.9	490	107	21.8	18.3	25.8
Vomiting	Total	914	131	14.3	12.1	16.8	490	80	16.3	13.2	19.9
	Grade 3	914	18	2.0	1.2	3.1	490	12	2.4	1.3	4.2
	Related	914	56	6.1	4.7	7.9	490	40	8.2	5.9	11.0

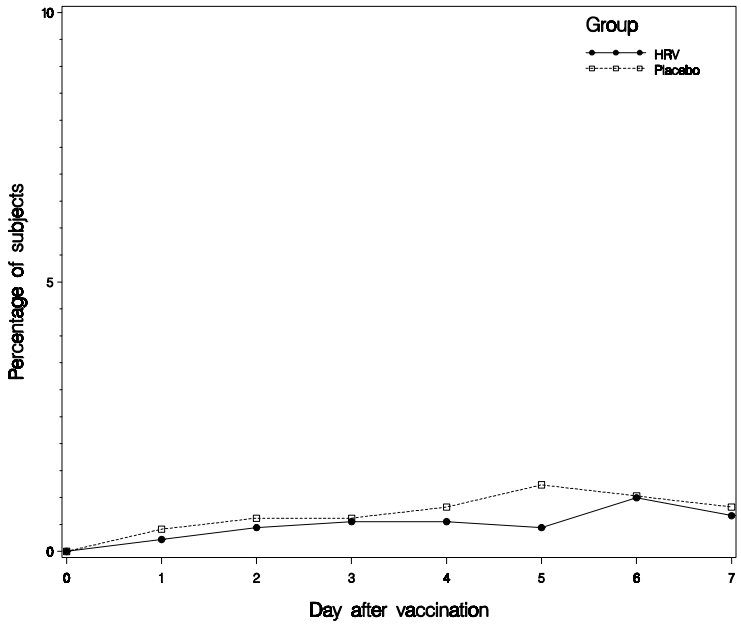
For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 336 Prevalence of diarrhea by day after Dose 1 of HRV/Placebo, during the solicited 8 days post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset



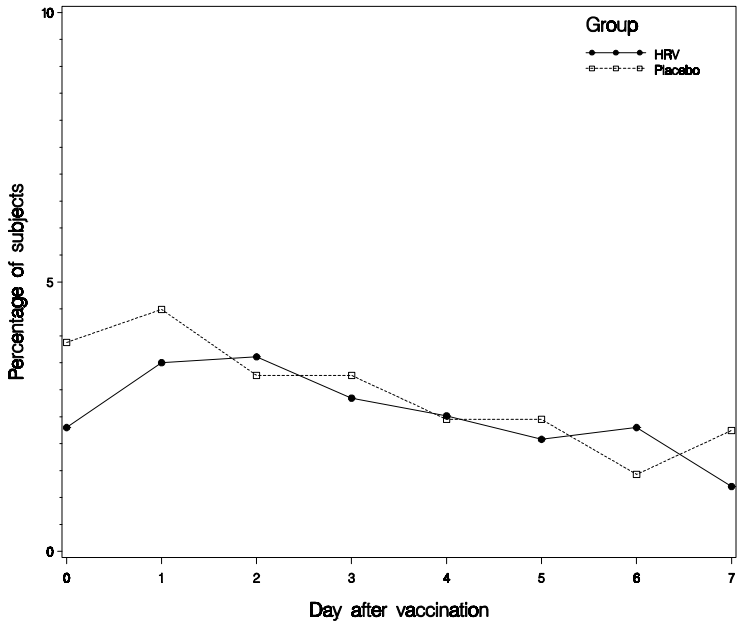
Day 0 = day of vaccination, Day 1 = one day after vaccination …
Percentage of subjects = percentage of subjects, among those having received the first dose of HRV/Placebo in the considered group, having diarrhea reported at day X of the post vaccination follow-up period

Supplement 337 Prevalence of diarrhea by day after Dose 2 of HRV/Placebo, during the solicited 8 days post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset



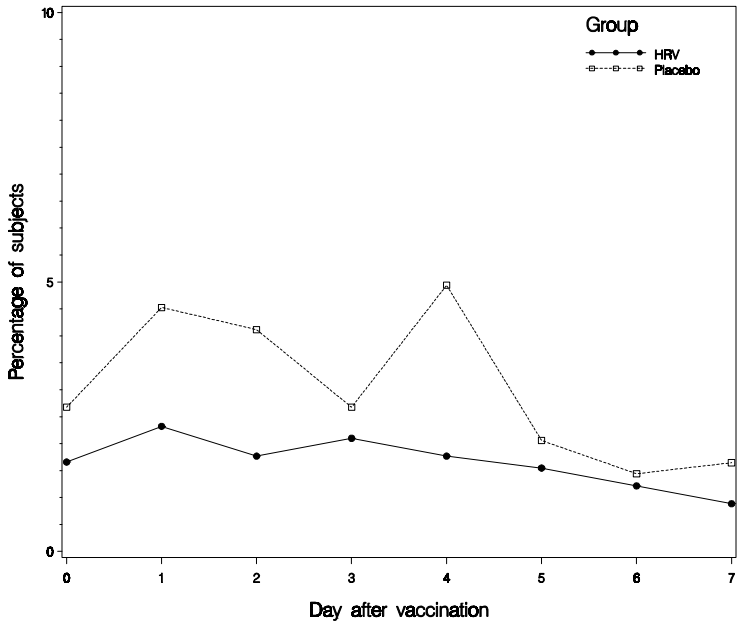
Day 0 = day of vaccination, Day 1 = one day after vaccination,…
Percentage of subjects = percentage of subjects, among those having received the second dose of HRV/Placebo in the considered group, having diarrhea reported at day X of the post vaccination follow-up period

Supplement 338 Prevalence of vomiting by day after Dose 1 of HRV/Placebo, during the solicited 8 days post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset



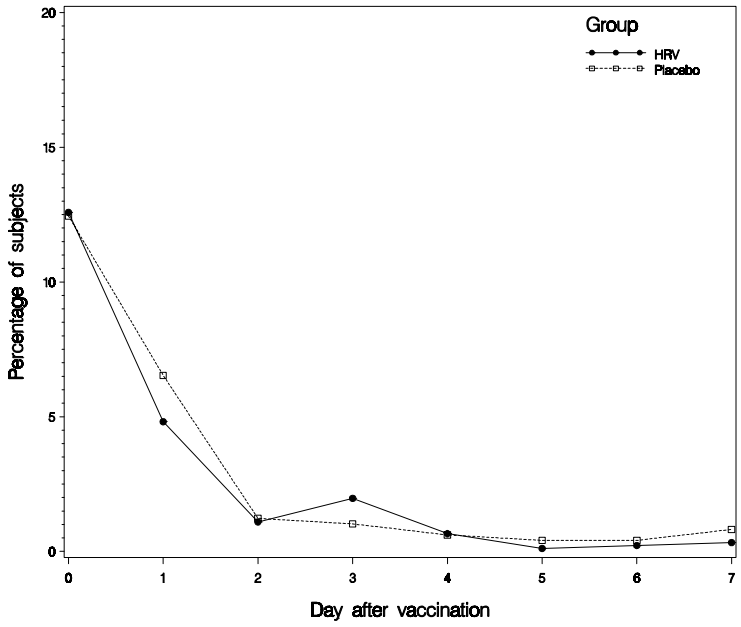
Day 0 = day of vaccination, Day 1 = one day after vaccination,…
Percentage of subjects = percentage of subjects, among those having received the first dose of HRV/Placebo in the considered group, having vomiting reported at day X of the post vaccination follow-up period

Supplement 339 Prevalence of vomiting by day after Dose 2 of HRV/Placebo, during the solicited 8 days post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset



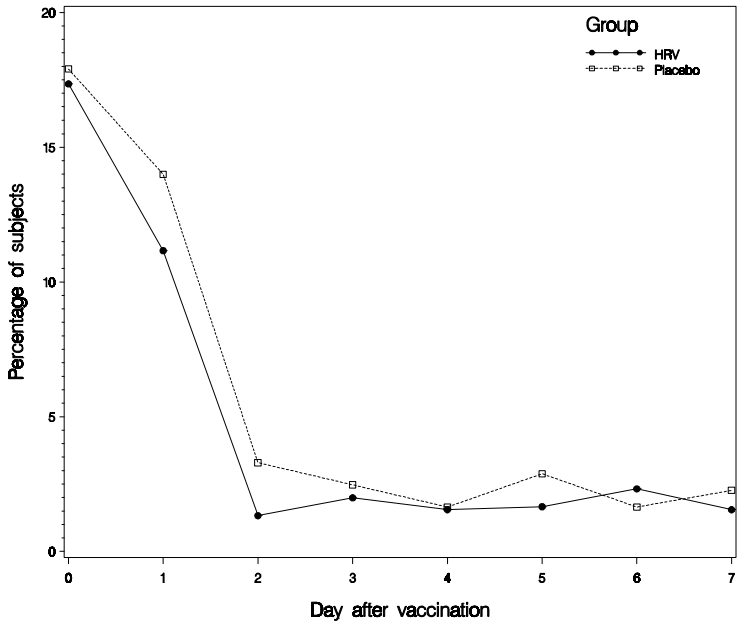
Day 0 = day of vaccination, Day 1 = one day after vaccination,…
Percentage of subjects = percentage of subjects, among those having received the second dose of HRV/Placebo in the considered group, having vomiting reported at day X of the post vaccination follow-up period

Supplement 340 Prevalence of fever by day after Dose 1 of HRV/Placebo, during the solicited 8 days post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset



Day 0 = day of vaccination, Day 1 = one day after vaccination,…
Percentage of subjects = percentage of subjects, among those having received the first dose of HRV/Placebo in the considered group, having fever reported at day X of the post vaccination follow-up period

Supplement 341 Prevalence of fever by day after Dose 2 of HRV/Placebo, during the solicited 8 days post vaccination follow-up period – Pooled countries – Total vaccinated cohort for the reactogenicity and immunogenicity subset



Day 0 = day of vaccination, Day 1 = one day after vaccination,…
Percentage of subjects = percentage of subjects, among those having received the second dose of HRV/Placebo in the related group, having fever reported at day X of the post vaccination follow-up period

Supplement 342 Percentage of subjects reporting each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for each HRV/placebo dose - Czech Republic – Total vaccinated cohort

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	199	53	26.6	20.6	33.3	100	23	23.0	15.2	32.5
	Grade 3	199	1	0.5	0.0	2.8	100	0	0.0	0.0	3.6
	Related	199	12	6.0	3.2	10.3	100	5	5.0	1.6	11.3
Diarrhea	Total	199	4	2.0	0.6	5.1	100	5	5.0	1.6	11.3
	Grade 3	199	0	0.0	0.0	1.8	100	2	2.0	0.2	7.0
	Related	199	3	1.5	0.3	4.3	100	3	3.0	0.6	8.5
Fever	Total	199	26	13.1	8.7	18.6	100	17	17.0	10.2	25.8
	Grade 3	199	0	0.0	0.0	1.8	100	0	0.0	0.0	3.6
	Related	199	20	10.1	6.2	15.1	100	12	12.0	6.4	20.0
Irritability/Fussiness	Total	199	83	41.7	34.8	48.9	100	39	39.0	29.4	49.3
	Grade 3	199	4	2.0	0.6	5.1	100	3	3.0	0.6	8.5
	Related	199	51	25.6	19.7	32.3	100	25	25.0	16.9	34.7
Loss of appetite	Total	199	17	8.5	5.1	13.3	100	13	13.0	7.1	21.2
	Grade 3	199	0	0.0	0.0	1.8	100	0	0.0	0.0	3.6
	Related	199	10	5.0	2.4	9.0	100	10	10.0	4.9	17.6
Vomiting	Total	199	16	8.0	4.7	12.7	100	8	8.0	3.5	15.2
	Grade 3	199	1	0.5	0.0	2.8	100	0	0.0	0.0	3.6
	Related	199	7	3.5	1.4	7.1	100	3	3.0	0.6	8.5
Dose 2											
Cough/Runny nose	Total	198	45	22.7	17.1	29.2	100	27	27.0	18.6	36.8
	Grade 3	198	0	0.0	0.0	1.8	100	0	0.0	0.0	3.6
	Related	198	10	5.1	2.4	9.1	100	9	9.0	4.2	16.4
Diarrhea	Total	198	4	2.0	0.6	5.1	100	2	2.0	0.2	7.0
	Grade 3	198	2	1.0	0.1	3.6	100	2	2.0	0.2	7.0
	Related	198	0	0.0	0.0	1.8	100	2	2.0	0.2	7.0
Fever	Total	198	39	19.7	14.4	25.9	100	25	25.0	16.9	34.7
	Grade 3	198	0	0.0	0.0	1.8	100	1	1.0	0.0	5.4
	Related	198	31	15.7	10.9	21.5	100	22	22.0	14.3	31.4
Irritability/Fussiness	Total	198	58	29.3	23.1	36.2	100	32	32.0	23.0	42.1
	Grade 3	198	5	2.5	0.8	5.8	100	1	1.0	0.0	5.4
	Related	198	37	18.7	13.5	24.8	100	19	19.0	11.8	28.1
Loss of appetite	Total	198	16	8.1	4.7	12.8	100	11	11.0	5.6	18.8
	Grade 3	198	0	0.0	0.0	1.8	100	1	1.0	0.0	5.4
	Related	198	11	5.6	2.8	9.7	100	8	8.0	3.5	15.2
Vomiting	Total	198	5	2.5	0.8	5.8	100	6	6.0	2.2	12.6
	Grade 3	198	0	0.0	0.0	1.8	100	1	1.0	0.0	5.4
	Related	198	1	0.5	0.0	2.8	100	3	3.0	0.6	8.5

N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 343 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - Czech Republic – Total vaccinated cohort

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose											
Cough/Runny nose	Total	397	98	24.7	20.5	29.2	200	50	25.0	19.2	31.6
	Grade 3	397	1	0.3	0.0	1.4	200	0	0.0	0.0	1.8
	Related	397	22	5.5	3.5	8.3	200	14	7.0	3.9	11.5
Diarrhea	Total	397	8	2.0	0.9	3.9	200	7	3.5	1.4	7.1
	Grade 3	397	2	0.5	0.1	1.8	200	4	2.0	0.5	5.0
	Related	397	3	0.8	0.2	2.2	200	5	2.5	0.8	5.7
Fever	Total	397	65	16.4	12.9	20.4	200	42	21.0	15.6	27.3
	Grade 3	397	0	0.0	0.0	0.9	200	1	0.5	0.0	2.8
	Related	397	51	12.8	9.7	16.5	200	34	17.0	12.1	22.9
Irritability/Fussiness	Total	397	141	35.5	30.8	40.4	200	71	35.5	28.9	42.6
	Grade 3	397	9	2.3	1.0	4.3	200	4	2.0	0.5	5.0
	Related	397	88	22.2	18.2	26.6	200	44	22.0	16.5	28.4
Loss of appetite	Total	397	33	8.3	5.8	11.5	200	24	12.0	7.8	17.3
	Grade 3	397	0	0.0	0.0	0.9	200	1	0.5	0.0	2.8
	Related	397	21	5.3	3.3	8.0	200	18	9.0	5.4	13.9
Vomiting	Total	397	21	5.3	3.3	8.0	200	14	7.0	3.9	11.5
	Grade 3	397	1	0.3	0.0	1.4	200	1	0.5	0.0	2.8
	Related	397	8	2.0	0.9	3.9	200	6	3.0	1.1	6.4
Overall/subject											
Cough/Runny nose	Total	199	76	38.2	31.4	45.3	100	39	39.0	29.4	49.3
	Grade 3	199	1	0.5	0.0	2.8	100	0	0.0	0.0	3.6
	Related	199	21	10.6	6.7	15.7	100	13	13.0	7.1	21.2
Diarrhea	Total	199	8	4.0	1.8	7.8	100	7	7.0	2.9	13.9
	Grade 3	199	2	1.0	0.1	3.6	100	4	4.0	1.1	9.9
	Related	199	3	1.5	0.3	4.3	100	5	5.0	1.6	11.3
Fever	Total	199	56	28.1	22.0	34.9	100	36	36.0	26.6	46.2
	Grade 3	199	0	0.0	0.0	1.8	100	1	1.0	0.0	5.4
	Related	199	45	22.6	17.0	29.1	100	30	30.0	21.2	40.0
Irritability/Fussiness	Total	199	103	51.8	44.6	58.9	100	52	52.0	41.8	62.1
	Grade 3	199	8	4.0	1.8	7.8	100	4	4.0	1.1	9.9
	Related	199	73	36.7	30.0	43.8	100	36	36.0	26.6	46.2
Loss of appetite	Total	199	28	14.1	9.6	19.7	100	21	21.0	13.5	30.3
	Grade 3	199	0	0.0	0.0	1.8	100	1	1.0	0.0	5.4
	Related	199	20	10.1	6.2	15.1	100	17	17.0	10.2	25.8
Vomiting	Total	199	20	10.1	6.2	15.1	100	11	11.0	5.6	18.8
	Grade 3	199	1	0.5	0.0	2.8	100	1	1.0	0.0	5.4
	Related	199	8	4.0	1.8	7.8	100	5	5.0	1.6	11.3

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 344 Percentage of subjects reporting each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for each HRV/placebo dose - Finland – Total vaccinated cohort for the reactogenicity and immunogenicity subset

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	186	50	26.9	20.7	33.9	114	32	28.1	20.1	37.3
	Grade 3	186	0	0.0	0.0	2.0	114	0	0.0	0.0	3.2
	Related	186	10	5.4	2.6	9.7	114	5	4.4	1.4	9.9
Diarrhea	Total	186	7	3.8	1.5	7.6	114	1	0.9	0.0	4.8
	Grade 3	186	0	0.0	0.0	2.0	114	0	0.0	0.0	3.2
	Related	186	5	2.7	0.9	6.2	114	1	0.9	0.0	4.8
Fever	Total	186	55	29.6	23.1	36.7	114	29	25.4	17.7	34.4
	Grade 3	186	0	0.0	0.0	2.0	114	0	0.0	0.0	3.2
	Related	186	46	24.7	18.7	31.6	114	23	20.2	13.2	28.7
Irritability/Fussiness	Total	186	134	72.0	65.0	78.4	114	90	78.9	70.3	86.0
	Grade 3	186	6	3.2	1.2	6.9	114	6	5.3	2.0	11.1
	Related	186	101	54.3	46.9	61.6	114	72	63.2	53.6	72.0
Loss of appetite	Total	186	51	27.4	21.1	34.4	114	29	25.4	17.7	34.4
	Grade 3	186	0	0.0	0.0	2.0	114	0	0.0	0.0	3.2
	Related	186	36	19.4	13.9	25.8	114	23	20.2	13.2	28.7
Vomiting	Total	186	23	12.4	8.0	18.0	114	12	10.5	5.6	17.7
	Grade 3	186	2	1.1	0.1	3.8	114	2	1.8	0.2	6.2
	Related	186	14	7.5	4.2	12.3	114	8	7.0	3.1	13.4
Dose 2											
Cough/Runny nose	Total	184	69	37.5	30.5	44.9	113	48	42.5	33.2	52.1
	Grade 3	184	4	2.2	0.6	5.5	113	0	0.0	0.0	3.2
	Related	184	9	4.9	2.3	9.1	113	8	7.1	3.1	13.5
Diarrhea	Total	184	2	1.1	0.1	3.9	113	3	2.7	0.6	7.6
	Grade 3	184	0	0.0	0.0	2.0	113	2	1.8	0.2	6.2
	Related	184	1	0.5	0.0	3.0	113	2	1.8	0.2	6.2
Fever	Total	184	79	42.9	35.7	50.4	113	47	41.6	32.4	51.2
	Grade 3	184	0	0.0	0.0	2.0	113	1	0.9	0.0	4.8
	Related	184	47	25.5	19.4	32.5	113	21	18.6	11.9	27.0
Irritability/Fussiness	Total	184	121	65.8	58.4	72.6	113	83	73.5	64.3	81.3
	Grade 3	184	6	3.3	1.2	7.0	113	3	2.7	0.6	7.6
	Related	184	75	40.8	33.6	48.2	113	45	39.8	30.7	49.5
Loss of appetite	Total	184	43	23.4	17.5	30.2	113	33	29.2	21.0	38.5
	Grade 3	184	1	0.5	0.0	3.0	113	0	0.0	0.0	3.2
	Related	184	28	15.2	10.4	21.2	113	19	16.8	10.4	25.0
Vomiting	Total	184	17	9.2	5.5	14.4	113	13	11.5	6.3	18.9
	Grade 3	184	1	0.5	0.0	3.0	113	3	2.7	0.6	7.6
	Related	184	7	3.8	1.5	7.7	113	8	7.1	3.1	13.5

N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 345 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - Finland – Total vaccinated cohort for the reactogenicity and immunogenicity subset

Overall/dose											
Cough/Runny nose	**Total**	370	119	32.2	27.4	37.2	227	80	35.2	29.0	41.8
	Grade 3	370	4	1.1	0.3	2.7	227	0	0.0	0.0	1.6
	Related	370	19	5.1	3.1	7.9	227	13	5.7	3.1	9.6
Diarrhea	**Total**	370	9	2.4	1.1	4.6	227	4	1.8	0.5	4.5
	Grade 3	370	0	0.0	0.0	1.0	227	2	0.9	0.1	3.1
	Related	370	6	1.6	0.6	3.5	227	3	1.3	0.3	3.8
Fever	**Total**	370	134	36.2	31.3	41.3	227	76	33.5	27.4	40.0
	Grade 3	370	0	0.0	0.0	1.0	227	1	0.4	0.0	2.4
	Related	370	93	25.1	20.8	29.9	227	44	19.4	14.5	25.1
Irritability/Fussiness	**Total**	370	255	68.9	63.9	73.6	227	173	76.2	70.1	81.6
	Grade 3	370	12	3.2	1.7	5.6	227	9	4.0	1.8	7.4
	Related	370	176	47.6	42.4	52.8	227	117	51.5	44.8	58.2
Loss of appetite	**Total**	370	94	25.4	21.0	30.2	227	62	27.3	21.6	33.6
	Grade 3	370	1	0.3	0.0	1.5	227	0	0.0	0.0	1.6
	Related	370	64	17.3	13.6	21.5	227	42	18.5	13.7	24.2
Vomiting	**Total**	370	40	10.8	7.8	14.4	227	25	11.0	7.3	15.8
	Grade 3	370	3	0.8	0.2	2.4	227	5	2.2	0.7	5.1
	Related	370	21	5.7	3.5	8.5	227	16	7.0	4.1	11.2
Overall/subject											
Cough/Runny nose	**Total**	186	94	50.5	43.1	57.9	114	64	56.1	46.5	65.4
	Grade 3	186	4	2.2	0.6	5.4	114	0	0.0	0.0	3.2
	Related	186	14	7.5	4.2	12.3	114	11	9.6	4.9	16.6
Diarrhea	**Total**	186	9	4.8	2.2	9.0	114	4	3.5	1.0	8.7
	Grade 3	186	0	0.0	0.0	2.0	114	2	1.8	0.2	6.2
	Related	186	6	3.2	1.2	6.9	114	3	2.6	0.5	7.5
Fever	**Total**	186	98	52.7	45.3	60.0	114	61	53.5	43.9	62.9
	Grade 3	186	0	0.0	0.0	2.0	114	1	0.9	0.0	4.8
	Related	186	70	37.6	30.7	45.0	114	36	31.6	23.2	40.9
Irritability/Fussiness	**Total**	186	151	81.2	74.8	86.5	114	103	90.4	83.4	95.1
	Grade 3	186	11	5.9	3.0	10.3	114	8	7.0	3.1	13.4
	Related	186	117	62.9	55.5	69.9	114	79	69.3	60.0	77.6
Loss of appetite	**Total**	186	76	40.9	33.7	48.3	114	50	43.9	34.6	53.5
	Grade 3	186	1	0.5	0.0	3.0	114	0	0.0	0.0	3.2
	Related	186	53	28.5	22.1	35.6	114	34	29.8	21.6	39.1
Vomiting	**Total**	186	32	17.2	12.1	23.4	114	20	17.5	11.1	25.8
	Grade 3	186	3	1.6	0.3	4.6	114	5	4.4	1.4	9.9
	Related	186	18	9.7	5.8	14.9	114	13	11.4	6.2	18.7

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 346 Percentage of subjects reporting each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for each HRV/placebo dose - France – Total vaccinated cohort

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	95	23	24.2	16.0	34.1	51	7	13.7	5.7	26.3
	Grade 3	95	0	0.0	0.0	3.8	51	0	0.0	0.0	7.0
	Related	95	1	1.1	0.0	5.7	51	1	2.0	0.0	10.4
Diarrhea	Total	95	3	3.2	0.7	9.0	51	1	2.0	0.0	10.4
	Grade 3	95	0	0.0	0.0	3.8	51	1	2.0	0.0	10.4
	Related	95	2	2.1	0.3	7.4	51	1	2.0	0.0	10.4
Fever	Total	95	25	26.3	17.8	36.4	51	10	19.6	9.8	33.1
	Grade 3	95	0	0.0	0.0	3.8	51	0	0.0	0.0	7.0
	Related	95	19	20.0	12.5	29.5	51	8	15.7	7.0	28.6
Irritability/Fussiness	Total	95	51	53.7	43.2	64.0	51	29	56.9	42.2	70.7
	Grade 3	95	1	1.1	0.0	5.7	51	3	5.9	1.2	16.2
	Related	95	29	30.5	21.5	40.8	51	20	39.2	25.8	53.9
Loss of appetite	Total	95	23	24.2	16.0	34.1	51	10	19.6	9.8	33.1
	Grade 3	95	0	0.0	0.0	3.8	51	0	0.0	0.0	7.0
	Related	95	11	11.6	5.9	19.8	51	8	15.7	7.0	28.6
Vomiting	Total	95	9	9.5	4.4	17.2	51	4	7.8	2.2	18.9
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	0	0.0	0.0	3.8	51	2	3.9	0.5	13.5
Dose 2											
Cough/Runny nose	Total	95	21	22.1	14.2	31.8	51	13	25.5	14.3	39.6
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	3	3.2	0.7	9.0	51	1	2.0	0.0	10.4
Diarrhea	Total	95	3	3.2	0.7	9.0	51	0	0.0	0.0	7.0
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
Fever	Total	95	32	33.7	24.3	44.1	51	12	23.5	12.8	37.5
	Grade 3	95	0	0.0	0.0	3.8	51	0	0.0	0.0	7.0
	Related	95	22	23.2	15.1	32.9	51	11	21.6	11.3	35.3
Irritability/Fussiness	Total	95	42	44.2	34.0	54.8	51	24	47.1	32.9	61.5
	Grade 3	95	3	3.2	0.7	9.0	51	1	2.0	0.0	10.4
	Related	95	26	27.4	18.7	37.5	51	12	23.5	12.8	37.5
Loss of appetite	Total	95	26	27.4	18.7	37.5	51	12	23.5	12.8	37.5
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	12	12.6	6.7	21.0	51	4	7.8	2.2	18.9
Vomiting	Total	95	2	2.1	0.3	7.4	51	4	7.8	2.2	18.9
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	0	0.0	0.0	3.8	51	0	0.0	0.0	7.0

N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 347 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - France – Total vaccinated cohort

Overall/dose											
Cough/Runny nose	**Total**	190	44	23.2	17.4	29.8	102	20	19.6	12.4	28.6
	Grade 3	190	1	0.5	0.0	2.9	102	0	0.0	0.0	3.6
	Related	190	4	2.1	0.6	5.3	102	2	2.0	0.2	6.9
Diarrhea	**Total**	190	6	3.2	1.2	6.7	102	1	1.0	0.0	5.3
	Grade 3	190	1	0.5	0.0	2.9	102	1	1.0	0.0	5.3
	Related	190	3	1.6	0.3	4.5	102	1	1.0	0.0	5.3
Fever	**Total**	190	57	30.0	23.6	37.1	102	22	21.6	14.0	30.8
	Grade 3	190	0	0.0	0.0	1.9	102	0	0.0	0.0	3.6
	Related	190	41	21.6	16.0	28.1	102	19	18.6	11.6	27.6
Irritability/Fussiness	**Total**	190	93	48.9	41.6	56.3	102	53	52.0	41.8	62.0
	Grade 3	190	4	2.1	0.6	5.3	102	4	3.9	1.1	9.7
	Related	190	55	28.9	22.6	36.0	102	32	31.4	22.5	41.3
Loss of appetite	**Total**	190	49	25.8	19.7	32.6	102	22	21.6	14.0	30.8
	Grade 3	190	1	0.5	0.0	2.9	102	0	0.0	0.0	3.6
	Related	190	23	12.1	7.8	17.6	102	12	11.8	6.2	19.6
Vomiting	**Total**	190	11	5.8	2.9	10.1	102	8	7.8	3.4	14.9
	Grade 3	190	2	1.1	0.1	3.8	102	0	0.0	0.0	3.6
	Related	190	0	0.0	0.0	1.9	102	2	2.0	0.2	6.9
Overall/subject											
Cough/Runny nose	**Total**	95	36	37.9	28.1	48.4	51	18	35.3	22.4	49.9
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	4	4.2	1.2	10.4	51	1	2.0	0.0	10.4
Diarrhea	**Total**	95	5	5.3	1.7	11.9	51	1	2.0	0.0	10.4
	Grade 3	95	1	1.1	0.0	5.7	51	1	2.0	0.0	10.4
	Related	95	3	3.2	0.7	9.0	51	1	2.0	0.0	10.4
Fever	**Total**	95	42	44.2	34.0	54.8	51	19	37.3	24.1	51.9
	Grade 3	95	0	0.0	0.0	3.8	51	0	0.0	0.0	7.0
	Related	95	32	33.7	24.3	44.1	51	16	31.4	19.1	45.9
Irritability/Fussiness	**Total**	95	62	65.3	54.8	74.7	51	35	68.6	54.1	80.9
	Grade 3	95	4	4.2	1.2	10.4	51	4	7.8	2.2	18.9
	Related	95	45	47.4	37.0	57.9	51	23	45.1	31.1	59.7
Loss of appetite	**Total**	95	36	37.9	28.1	48.4	51	19	37.3	24.1	51.9
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	17	17.9	10.8	27.1	51	10	19.6	9.8	33.1
Vomiting	**Total**	95	10	10.5	5.2	18.5	51	6	11.8	4.4	23.9
	Grade 3	95	1	1.1	0.0	5.7	51	0	0.0	0.0	7.0
	Related	95	0	0.0	0.0	3.8	51	2	3.9	0.5	13.5

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 348 Percentage of subjects reporting each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for each HRV/placebo dose - Germany – Total vaccinated cohort

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	190	37	19.5	14.1	25.8	99	18	18.2	11.1	27.2
	Grade 3	190	2	1.1	0.1	3.8	99	1	1.0	0.0	5.5
	Related	190	9	4.7	2.2	8.8	99	4	4.0	1.1	10.0
Diarrhea	Total	190	2	1.1	0.1	3.8	99	2	2.0	0.2	7.1
	Grade 3	190	0	0.0	0.0	1.9	99	0	0.0	0.0	3.7
	Related	190	2	1.1	0.1	3.8	99	1	1.0	0.0	5.5
Fever	Total	190	34	17.9	12.7	24.1	99	23	23.2	15.3	32.8
	Grade 3	190	0	0.0	0.0	1.9	99	0	0.0	0.0	3.7
	Related	190	29	15.3	10.5	21.2	99	16	16.2	9.5	24.9
Irritability/Fussiness	Total	190	70	36.8	30.0	44.1	99	30	30.3	21.5	40.4
	Grade 3	190	5	2.6	0.9	6.0	99	5	5.1	1.7	11.4
	Related	190	33	17.4	12.3	23.5	99	16	16.2	9.5	24.9
Loss of appetite	Total	190	41	21.6	16.0	28.1	99	18	18.2	11.1	27.2
	Grade 3	190	0	0.0	0.0	1.9	99	1	1.0	0.0	5.5
	Related	190	18	9.5	5.7	14.6	99	11	11.1	5.7	19.0
Vomiting	Total	190	21	11.1	7.0	16.4	99	10	10.1	5.0	17.8
	Grade 3	190	2	1.1	0.1	3.8	99	2	2.0	0.2	7.1
	Related	190	7	3.7	1.5	7.4	99	1	1.0	0.0	5.5
Dose 2											
Cough/Runny nose	Total	187	41	21.9	16.2	28.5	99	20	20.2	12.8	29.5
	Grade 3	187	1	0.5	0.0	2.9	99	1	1.0	0.0	5.5
	Related	187	8	4.3	1.9	8.3	99	2	2.0	0.2	7.1
Diarrhea	Total	187	1	0.5	0.0	2.9	99	1	1.0	0.0	5.5
	Grade 3	187	0	0.0	0.0	2.0	99	0	0.0	0.0	3.7
	Related	187	0	0.0	0.0	2.0	99	1	1.0	0.0	5.5
Fever	Total	187	48	25.7	19.6	32.6	99	31	31.3	22.4	41.4
	Grade 3	187	1	0.5	0.0	2.9	99	2	2.0	0.2	7.1
	Related	187	35	18.7	13.4	25.1	99	23	23.2	15.3	32.8
Irritability/Fussiness	Total	187	56	29.9	23.5	37.1	99	29	29.3	20.6	39.3
	Grade 3	187	2	1.1	0.1	3.8	99	1	1.0	0.0	5.5
	Related	187	29	15.5	10.6	21.5	99	17	17.2	10.3	26.1
Loss of appetite	Total	187	35	18.7	13.4	25.1	99	14	14.1	8.0	22.6
	Grade 3	187	0	0.0	0.0	2.0	99	0	0.0	0.0	3.7
	Related	187	18	9.6	5.8	14.8	99	8	8.1	3.6	15.3
Vomiting	Total	187	12	6.4	3.4	10.9	99	9	9.1	4.2	16.6
	Grade 3	187	2	1.1	0.1	3.8	99	3	3.0	0.6	8.6
	Related	187	3	1.6	0.3	4.6	99	5	5.1	1.7	11.4

N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 349 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - Germany – Total vaccinated cohort

Overall/dose											
Cough/Runny nose	**Total**	377	78	20.7	16.7	25.1	198	38	19.2	14.0	25.4
	Grade 3	377	3	0.8	0.2	2.3	198	2	1.0	0.1	3.6
	Related	377	17	4.5	2.6	7.1	198	6	3.0	1.1	6.5
Diarrhea	**Total**	377	3	0.8	0.2	2.3	198	3	1.5	0.3	4.4
	Grade 3	377	0	0.0	0.0	1.0	198	0	0.0	0.0	1.8
	Related	377	2	0.5	0.1	1.9	198	2	1.0	0.1	3.6
Fever	**Total**	377	82	21.8	17.7	26.3	198	54	27.3	21.2	34.0
	Grade 3	377	1	0.3	0.0	1.5	198	2	1.0	0.1	3.6
	Related	377	64	17.0	13.3	21.2	198	39	19.7	14.4	25.9
Irritability/Fussiness	**Total**	377	126	33.4	28.7	38.4	198	59	29.8	23.5	36.7
	Grade 3	377	7	1.9	0.7	3.8	198	6	3.0	1.1	6.5
	Related	377	62	16.4	12.8	20.6	198	33	16.7	11.8	22.6
Loss of appetite	**Total**	377	76	20.2	16.2	24.6	198	32	16.2	11.3	22.0
	Grade 3	377	0	0.0	0.0	1.0	198	1	0.5	0.0	2.8
	Related	377	36	9.5	6.8	13.0	198	19	9.6	5.9	14.6
Vomiting	**Total**	377	33	8.8	6.1	12.1	198	19	9.6	5.9	14.6
	Grade 3	377	4	1.1	0.3	2.7	198	5	2.5	0.8	5.8
	Related	377	10	2.7	1.3	4.8	198	6	3.0	1.1	6.5
Overall/subject											
Cough/Runny nose	**Total**	190	61	32.1	25.5	39.2	99	31	31.3	22.4	41.4
	Grade 3	190	3	1.6	0.3	4.5	99	2	2.0	0.2	7.1
	Related	190	16	8.4	4.9	13.3	99	5	5.1	1.7	11.4
Diarrhea	**Total**	190	3	1.6	0.3	4.5	99	3	3.0	0.6	8.6
	Grade 3	190	0	0.0	0.0	1.9	99	0	0.0	0.0	3.7
	Related	190	2	1.1	0.1	3.8	99	2	2.0	0.2	7.1
Fever	**Total**	190	56	29.5	23.1	36.5	99	41	41.4	31.6	51.8
	Grade 3	190	1	0.5	0.0	2.9	99	2	2.0	0.2	7.1
	Related	190	46	24.2	18.3	30.9	99	30	30.3	21.5	40.4
Irritability/Fussiness	**Total**	190	85	44.7	37.5	52.1	99	40	40.4	30.7	50.7
	Grade 3	190	6	3.2	1.2	6.7	99	6	6.1	2.3	12.7
	Related	190	42	22.1	16.4	28.7	99	27	27.3	18.8	37.1
Loss of appetite	**Total**	190	54	28.4	22.1	35.4	99	27	27.3	18.8	37.1
	Grade 3	190	0	0.0	0.0	1.9	99	1	1.0	0.0	5.5
	Related	190	30	15.8	10.9	21.8	99	17	17.2	10.3	26.1
Vomiting	**Total**	190	26	13.7	9.1	19.4	99	15	15.2	8.7	23.8
	Grade 3	190	4	2.1	0.6	5.3	99	4	4.0	1.1	10.0
	Related	190	9	4.7	2.2	8.8	99	5	5.1	1.7	11.4

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 350 Percentage of subjects reporting each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for each HRV/placebo dose - Italy – Total vaccinated cohort

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	15	4	26.7	7.8	55.1	10	3	30.0	6.7	65.2
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
Diarrhea	Total	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
Fever	Total	15	4	26.7	7.8	55.1	10	0	0.0	0.0	30.8
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
Irritability/Fussiness	Total	15	5	33.3	11.8	61.6	10	7	70.0	34.8	93.3
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	1	10.0	0.3	44.5
Loss of appetite	Total	15	2	13.3	1.7	40.5	10	2	20.0	2.5	55.6
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
Vomiting	Total	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
Dose 2											
Cough/Runny nose	Total	15	5	33.3	11.8	61.6	10	1	10.0	0.3	44.5
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
Diarrhea	Total	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
Fever	Total	15	6	40.0	16.3	67.7	10	3	30.0	6.7	65.2
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	2	20.0	2.5	55.6
Irritability/Fussiness	Total	15	9	60.0	32.3	83.7	10	3	30.0	6.7	65.2
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
Loss of appetite	Total	15	3	20.0	4.3	48.1	10	3	30.0	6.7	65.2
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
Vomiting	Total	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
	Grade 3	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8

N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 351 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - Italy – Total vaccinated cohort

Overall/dose											
Cough/Runny nose	**Total**	30	9	30.0	14.7	49.4	20	4	20.0	5.7	43.7
	Grade 3	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
	Related	30	1	3.3	0.1	17.2	20	0	0.0	0.0	16.8
Diarrhea	**Total**	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
	Grade 3	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
	Related	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
Fever	**Total**	30	10	33.3	17.3	52.8	20	3	15.0	3.2	37.9
	Grade 3	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
	Related	30	1	3.3	0.1	17.2	20	2	10.0	1.2	31.7
Irritability/Fussiness	**Total**	30	14	46.7	28.3	65.7	20	10	50.0	27.2	72.8
	Grade 3	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
	Related	30	1	3.3	0.1	17.2	20	1	5.0	0.1	24.9
Loss of appetite	**Total**	30	5	16.7	5.6	34.7	20	5	25.0	8.7	49.1
	Grade 3	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
	Related	30	1	3.3	0.1	17.2	20	0	0.0	0.0	16.8
Vomiting	**Total**	30	1	3.3	0.1	17.2	20	0	0.0	0.0	16.8
	Grade 3	30	1	3.3	0.1	17.2	20	0	0.0	0.0	16.8
	Related	30	0	0.0	0.0	11.6	20	0	0.0	0.0	16.8
Overall/subject											
Cough/Runny nose	**Total**	15	8	53.3	26.6	78.7	10	3	30.0	6.7	65.2
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
Diarrhea	**Total**	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
Fever	**Total**	15	8	53.3	26.6	78.7	10	3	30.0	6.7	65.2
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	2	20.0	2.5	55.6
Irritability/Fussiness	**Total**	15	10	66.7	38.4	88.2	10	7	70.0	34.8	93.3
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	1	10.0	0.3	44.5
Loss of appetite	**Total**	15	4	26.7	7.8	55.1	10	4	40.0	12.2	73.8
	Grade 3	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8
	Related	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
Vomiting	**Total**	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
	Grade 3	15	1	6.7	0.2	31.9	10	0	0.0	0.0	30.8
	Related	15	0	0.0	0.0	21.8	10	0	0.0	0.0	30.8

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 352 Percentage of subjects reporting each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for each HRV/placebo dose - Spain – Total vaccinated cohort

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/Runny nose	Total	229	54	23.6	18.2	29.6	116	34	29.3	21.2	38.5
	Grade 3	229	4	1.7	0.5	4.4	116	1	0.9	0.0	4.7
	Related	229	26	11.4	7.6	16.2	116	14	12.1	6.8	19.4
Diarrhea	Total	229	8	3.5	1.5	6.8	116	2	1.7	0.2	6.1
	Grade 3	229	3	1.3	0.3	3.8	116	1	0.9	0.0	4.7
	Related	229	6	2.6	1.0	5.6	116	1	0.9	0.0	4.7
Fever	Total	229	22	9.6	6.1	14.2	116	12	10.3	5.5	17.4
	Grade 3	229	0	0.0	0.0	1.6	116	0	0.0	0.0	3.1
	Related	229	18	7.9	4.7	12.1	116	8	6.9	3.0	13.1
Irritability/Fussiness	Total	229	117	51.1	44.4	57.7	116	55	47.4	38.1	56.9
	Grade 3	229	7	3.1	1.2	6.2	116	2	1.7	0.2	6.1
	Related	229	85	37.1	30.8	43.7	116	37	31.9	23.6	41.2
Loss of appetite	Total	229	76	33.2	27.1	39.7	116	28	24.1	16.7	33.0
	Grade 3	229	4	1.7	0.5	4.4	116	0	0.0	0.0	3.1
	Related	229	51	22.3	17.1	28.2	116	19	16.4	10.2	24.4
Vomiting	Total	229	32	14.0	9.8	19.2	116	18	15.5	9.5	23.4
	Grade 3	229	4	1.7	0.5	4.4	116	2	1.7	0.2	6.1
	Related	229	16	7.0	4.0	11.1	116	10	8.6	4.2	15.3
Dose 2											
Cough/Runny nose	Total	226	53	23.5	18.1	29.5	113	40	35.4	26.6	45.0
	Grade 3	226	4	1.8	0.5	4.5	113	0	0.0	0.0	3.2
	Related	226	22	9.7	6.2	14.4	113	14	12.4	6.9	19.9
Diarrhea	Total	226	5	2.2	0.7	5.1	113	3	2.7	0.6	7.6
	Grade 3	226	3	1.3	0.3	3.8	113	2	1.8	0.2	6.2
	Related	226	4	1.8	0.5	4.5	113	3	2.7	0.6	7.6
Fever	Total	226	40	17.7	13.0	23.3	113	24	21.2	14.1	29.9
	Grade 3	226	1	0.4	0.0	2.4	113	0	0.0	0.0	3.2
	Related	226	29	12.8	8.8	17.9	113	16	14.2	8.3	22.0
Irritability/Fussiness	Total	226	104	46.0	39.4	52.8	113	44	38.9	29.9	48.6
	Grade 3	226	5	2.2	0.7	5.1	113	1	0.9	0.0	4.8
	Related	226	70	31.0	25.0	37.4	113	30	26.5	18.7	35.7
Loss of appetite	Total	226	72	31.9	25.8	38.4	113	29	25.7	17.9	34.7
	Grade 3	226	4	1.8	0.5	4.5	113	0	0.0	0.0	3.2
	Related	226	48	21.2	16.1	27.2	113	18	15.9	9.7	24.0
Vomiting	Total	226	16	7.1	4.1	11.2	113	14	12.4	6.9	19.9
	Grade 3	226	4	1.8	0.5	4.5	113	0	0.0	0.0	3.2
	Related	226	7	3.1	1.3	6.3	113	7	6.2	2.5	12.3

N = number of subjects having received the considered dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 353 Percentage of doses and of subjects having each solicited general symptom, including those graded 3 in intensity and those assessed as causally related to vaccination, reported during the solicited 8 days (Day 0 – Day 7) post vaccination follow-up period, for all HRV/placebo doses - Spain – Total vaccinated cohort

Overall/dose											
Cough/Runny nose	**Total**	455	107	23.5	19.7	27.7	229	74	32.3	26.3	38.8
	Grade 3	455	8	1.8	0.8	3.4	229	1	0.4	0.0	2.4
	Related	455	48	10.5	7.9	13.7	229	28	12.2	8.3	17.2
Diarrhea	**Total**	455	13	2.9	1.5	4.8	229	5	2.2	0.7	5.0
	Grade 3	455	6	1.3	0.5	2.8	229	3	1.3	0.3	3.8
	Related	455	10	2.2	1.1	4.0	229	4	1.7	0.5	4.4
Fever	**Total**	455	62	13.6	10.6	17.1	229	36	15.7	11.3	21.1
	Grade 3	455	1	0.2	0.0	1.2	229	0	0.0	0.0	1.6
	Related	455	47	10.3	7.7	13.5	229	24	10.5	6.8	15.2
Irritability/Fussiness	**Total**	455	221	48.6	43.9	53.3	229	99	43.2	36.7	49.9
	Grade 3	455	12	2.6	1.4	4.6	229	3	1.3	0.3	3.8
	Related	455	155	34.1	29.7	38.6	229	67	29.3	23.5	35.6
Loss of appetite	**Total**	455	148	32.5	28.2	37.0	229	57	24.9	19.4	31.0
	Grade 3	455	8	1.8	0.8	3.4	229	0	0.0	0.0	1.6
	Related	455	99	21.8	18.1	25.8	229	37	16.2	11.6	21.6
Vomiting	**Total**	455	48	10.5	7.9	13.7	229	32	14.0	9.8	19.2
	Grade 3	455	8	1.8	0.8	3.4	229	2	0.9	0.1	3.1
	Related	455	23	5.1	3.2	7.5	229	17	7.4	4.4	11.6
Overall/subject											
Cough/Runny nose	**Total**	229	91	39.7	33.4	46.4	116	50	43.1	33.9	52.6
	Grade 3	229	7	3.1	1.2	6.2	116	1	0.9	0.0	4.7
	Related	229	43	18.8	13.9	24.4	116	22	19.0	12.3	27.3
Diarrhea	**Total**	229	13	5.7	3.1	9.5	116	5	4.3	1.4	9.8
	Grade 3	229	6	2.6	1.0	5.6	116	3	2.6	0.5	7.4
	Related	229	10	4.4	2.1	7.9	116	4	3.4	0.9	8.6
Fever	**Total**	229	50	21.8	16.7	27.8	116	32	27.6	19.7	36.7
	Grade 3	229	1	0.4	0.0	2.4	116	0	0.0	0.0	3.1
	Related	229	40	17.5	12.8	23.0	116	23	19.8	13.0	28.3
Irritability/Fussiness	**Total**	229	156	68.1	61.7	74.1	116	71	61.2	51.7	70.1
	Grade 3	229	11	4.8	2.4	8.4	116	3	2.6	0.5	7.4
	Related	229	117	51.1	44.4	57.7	116	52	44.8	35.6	54.3
Loss of appetite	**Total**	229	112	48.9	42.3	55.6	116	40	34.5	25.9	43.9
	Grade 3	229	7	3.1	1.2	6.2	116	0	0.0	0.0	3.1
	Related	229	81	35.4	29.2	41.9	116	29	25.0	17.4	33.9
Vomiting	**Total**	229	42	18.3	13.5	24.0	116	28	24.1	16.7	33.0
	Grade 3	229	8	3.5	1.5	6.8	116	2	1.7	0.2	6.1
	Related	229	21	9.2	5.8	13.7	116	15	12.9	7.4	20.4

For overall/dose: N = total number of HRV/Placebo doses administered
n/% = number/percentage of doses followed by the specified symptom
For overall/subject: N = number of subjects having received at least one dose of HRV/Placebo
n/% = number/percentage of subjects reporting the specified symptom after any doses
Total = any occurrence of the specified symptom, irrespective of intensity grade and relationship to vaccination
Grade 3 = any occurrence of the specified symptom rated as grade 3
Related = any occurrence of the specified symptom assessed as causally related to the vaccination
95% CI: exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 354 Percentage of subjects with unsolicited AEs classified by MedDRA primary System Organ Class (SOC) from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

	HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	1686	63.7	61.9	65.6	828	61.4	58.8	64.0	2.29	-0.87	5.49	0.156
Blood and lymphatic system disorders (10005329)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
Congenital, familial and genetic disorders (10010331)	3	0.1	0.0	0.3	1	0.1	0.0	0.4	0.04	-0.31	0.27	0.711
Ear and labyrinth disorders (10013993)	4	0.2	0.0	0.4	1	0.1	0.0	0.4	0.08	-0.28	0.33	0.515
Eye disorders (10015919)	92	3.5	2.8	4.2	48	3.6	2.6	4.7	-0.08	-1.38	1.08	0.892
Gastrointestinal disorders (10017947)	379	14.3	13.0	15.7	171	12.7	11.0	14.6	1.64	-0.64	3.82	0.155
General disorders and administration site conditions (10018065)	1009	38.1	36.3	40.0	477	35.4	32.8	38.0	2.75	-0.43	5.88	0.089
Immune system disorders (10021428)	13	0.5	0.3	0.8	5	0.4	0.1	0.9	0.12	-0.41	0.53	0.591
Infections and infestations (10021881)	816	30.8	29.1	32.6	410	30.4	28.0	32.9	0.42	-2.62	3.42	0.784
Injury, poisoning and procedural complications (10022117)	4	0.2	0.0	0.4	4	0.3	0.1	0.8	-0.15	-0.62	0.15	0.331
Investigations (10022891)	3	0.1	0.0	0.3	1	0.1	0.0	0.4	0.04	-0.31	0.27	0.711
Metabolism and nutrition disorders (10027433)	33	1.2	0.9	1.7	15	1.1	0.6	1.8	0.13	-0.66	0.80	0.712
Musculoskeletal and connective tissue disorders (10028395)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Nervous system disorders (10029205)	40	1.5	1.1	2.1	28	2.1	1.4	3.0	-0.57	-1.56	0.27	0.191
Psychiatric disorders (10037175)	264	10.0	8.9	11.2	141	10.5	8.9	12.2	-0.48	-2.54	1.46	0.633
Reproductive system and breast disorders (10038604)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
Respiratory, thoracic and mediastinal disorders (10038738)	199	7.5	6.5	8.6	105	7.8	6.4	9.4	-0.27	-2.08	1.43	0.762
Skin and subcutaneous tissue disorders (10040785)	123	4.6	3.9	5.5	53	3.9	3.0	5.1	0.72	-0.67	1.98	0.297
Social circumstances (10041244)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
Surgical and medical procedures (10042613)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
Vascular disorders (10047065)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216

N=number of subjects having received at least one dose of HRV/placebo
n/%= number/percentage of subjects reporting at least one unsolicited adverse event in the specified primary SOC category within 31 days after any HRV/placebo doses
At least one symptom = number of subjects reporting at least one unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA SOC
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = result of the comparison between groups of the percentages of subjects reporting the specified unsolicited adverse event within 31 days after any doses, by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 were used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 355 Percentage of subjects with unsolicited AEs classified by MedDRA primary SOC and Preferred Term (PT) from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	
At least one symptom		1686	63.7	61.9	65.6	828	61.4	58.8	64.0	2.29	-0.87	5.49	0.156
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Lymphadenopathy (10025197)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Congenital, familial and genetic disorders (10010331)	Congenital labia pudendi adhesions (10050268)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Hydrocele (10020488)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Laryngomalacia (10060786)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
	Ear pruritus (10052138)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Eye disorders (10015919)	Conjunctivitis (10010741)	85	3.2	2.6	4.0	41	3.0	2.2	4.1	0.17	-1.05	1.26	0.770
	Eye discharge (10015915)	6	0.2	0.1	0.5	5	0.4	0.1	0.9	-0.14	-0.65	0.19	0.411
	Eye inflammation (10015943)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Eyelid oedema (10015993)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Keratitis (10023332)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Strabismus (10042159)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Gastrointestinal disorders (10017947)	Abdominal discomfort (10000059)	2	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.15	-0.58	0.09	0.214
	Abdominal distension (10000060)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Abdominal pain (10000081)	24	0.9	0.6	1.3	5	0.4	0.1	0.9	0.54	-0.03	1.04	0.059
	Abdominal pain upper (10000087)	37	1.4	1.0	1.9	19	1.4	0.9	2.2	-0.01	-0.88	0.72	0.977
	Abnormal faeces (10000133)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Anal fissure (10002153)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Anorectal disorder (10002644)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Aphthous stomatitis (10002958)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Constipation (10010774)	50	1.9	1.4	2.5	20	1.5	0.9	2.3	0.41	-0.50	1.20	0.355
	Diarrhea (10012735)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
	Dyspepsia (10013946)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Enterocolitis (10014893)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Flatulence (10016766)	100	3.8	3.1	4.6	33	2.4	1.7	3.4	1.33	0.17	2.40	0.027

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	%	**LL**	**UL**	
	Frequent bowel movements (10017367)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Gastrointestinal disorder (10017944)	77	2.9	2.3	3.6	37	2.7	1.9	3.8	0.17	-1.00	1.20	0.767
	Gastrooesophageal reflux disease (10017885)	6	0.2	0.1	0.5	5	0.4	0.1	0.9	-0.14	-0.65	0.19	0.411
	Haematochezia (10018836)	11	0.4	0.2	0.7	6	0.4	0.2	1.0	-0.03	-0.58	0.38	0.893
	Infantile colic (10021746)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Infantile spitting up (10063338)	12	0.5	0.2	0.8	8	0.6	0.3	1.2	-0.14	-0.74	0.31	0.553
	Infrequent bowel movements (10059158)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Inguinal hernia (10022016)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Intussusception (10022863)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Mucous stools (10028140)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Oesophagitis (10030216)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Painful defaecation (10055664)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Perianal erythema (10056273)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Rectal haemorrhage (10038063)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Regurgitation of food (10038288)	34	1.3	0.9	1.8	14	1.0	0.6	1.7	0.25	-0.53	0.91	0.499
	Salivary hypersecretion (10039424)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Stomatitis (10042128)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Teething (10043183)	56	2.1	1.6	2.7	24	1.8	1.1	2.6	0.34	-0.64	1.19	0.474
	Toothache (10044055)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Vomiting (10047700)	47	1.8	1.3	2.4	27	2.0	1.3	2.9	-0.23	-1.22	0.63	0.615
General disorders and administration site conditions (10018065)	Application site pain (10003051)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Chills (10008531)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Discomfort (10013082)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Fatigue (10016256)	45	1.7	1.2	2.3	24	1.8	1.1	2.6	-0.08	-1.03	0.74	0.855
	Ill-defined disorder (10061520)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Inflammation (10061218)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Influenza like illness (10022004)	17	0.6	0.4	1.0	6	0.4	0.2	1.0	0.20	-0.37	0.66	0.436
	Injection site erythema (10022061)	22	0.8	0.5	1.3	10	0.7	0.4	1.4	0.09	-0.59	0.64	0.764

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	%	**LL**	**UL**	
	Injection site haemorrhage (10022067)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Injection site induration (10022075)	14	0.5	0.3	0.9	5	0.4	0.1	0.9	0.16	-0.37	0.58	0.492
	Injection site inflammation (10022078)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Injection site irritation (10022079)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Injection site mass (10022081)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Injection site nodule (10057880)	5	0.2	0.1	0.4	6	0.4	0.2	1.0	-0.26	-0.79	0.09	0.144
	Injection site pain (10022086)	106	4.0	3.3	4.8	40	3.0	2.1	4.0	1.04	-0.21	2.18	0.098
	Injection site reaction (10022095)	16	0.6	0.3	1.0	7	0.5	0.2	1.1	0.09	-0.51	0.55	0.736
	Injection site swelling (10053425)	25	0.9	0.6	1.4	13	1.0	0.5	1.6	-0.02	-0.76	0.58	0.952
	Irritability (10022998)	555	21.0	19.4	22.6	229	17.0	15.0	19.1	3.99	1.41	6.48	0.003
	Malaise (10025482)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Mucous membrane disorder (10028133)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Oedema peripheral (10030124)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pain (10033371)	7	0.3	0.1	0.5	2	0.1	0.0	0.5	0.12	-0.29	0.42	0.464
	Pyrexia (10037660)	612	23.1	21.5	24.8	316	23.4	21.2	25.8	-0.31	-3.12	2.42	0.825
	Venipuncture site pain (10048823)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Immune system disorders (10021428)	Atopy (10003645)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
	Food allergy (10016946)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Hypersensitivity (10020751)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Milk allergy (10027633)	5	0.2	0.1	0.4	3	0.2	0.0	0.6	-0.03	-0.48	0.26	0.822
Infections and infestations (10021881)	Abscess (10000269)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Bronchiolitis (10006448)	33	1.2	0.9	1.7	20	1.5	0.9	2.3	-0.24	-1.11	0.49	0.537
	Bronchitis (10006451)	39	1.5	1.1	2.0	20	1.5	0.9	2.3	-0.01	-0.90	0.74	0.981
	Bronchitis acute (10006452)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Bronchopneumonia (10006469)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Campylobacter infection (10051226)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Candida nappy rash (10007135)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Candidiasis (10007152)	10	0.4	0.2	0.7	7	0.5	0.2	1.1	-0.14	-0.72	0.27	0.516
	Ear infection (10014011)	26	1.0	0.6	1.4	12	0.9	0.5	1.5	0.09	-0.63	0.69	0.776

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
	Eczema infected (10014199)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Enterovirus infection (10014909)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Exanthema subitum (10015586)	12	0.5	0.2	0.8	11	0.8	0.4	1.5	-0.36	-1.03	0.13	0.152
	Eye infection (10015929)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Eyelid infection (10015988)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Gastroenteritis (10017888)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Gastrointestinal infection (10017964)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Genital candidiasis (10018143)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Herpetic gingivostomatitis (10019996)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Impetigo (10021531)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Infection (10021789)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Influenza (10022000)	37	1.4	1.0	1.9	13	1.0	0.5	1.6	0.43	-0.34	1.10	0.243
	Injection site cellulitis (10050057)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Laryngitis (10023874)	18	0.7	0.4	1.1	7	0.5	0.2	1.1	0.16	-0.44	0.64	0.542
	Meningitis (10027199)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Nasopharyngitis (10028810)	28	1.1	0.7	1.5	17	1.3	0.7	2.0	-0.20	-1.02	0.46	0.566
	Oral candidiasis (10030963)	11	0.4	0.2	0.7	2	0.1	0.0	0.5	0.27	-0.15	0.62	0.161
	Oral fungal infection (10061324)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Otitis externa (10033072)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Otitis media (10033078)	126	4.8	4.0	5.6	69	5.1	4.0	6.4	-0.36	-1.86	1.02	0.621
	Otitis media acute (10033079)	5	0.2	0.1	0.4	1	0.1	0.0	0.4	0.11	-0.24	0.38	0.376
	Paronychia (10034016)	3	0.1	0.0	0.3	1	0.1	0.0	0.4	0.04	-0.31	0.27	0.711
	Perianal abscess (10034447)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pertussis (10034738)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pharyngitis (10034835)	14	0.5	0.3	0.9	7	0.5	0.2	1.1	0.01	-0.58	0.46	0.968
	Pneumonia (10035664)	4	0.2	0.0	0.4	2	0.1	0.0	0.5	0.00	-0.40	0.27	0.983
	Pneumonia respiratory syncytial viral (10035732)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Pyelonephritis (10037596)	5	0.2	0.1	0.4	1	0.1	0.0	0.4	0.11	-0.24	0.38	0.376
	Pyelonephritis acute (10037597)	4	0.2	0.0	0.4	1	0.1	0.0	0.4	0.08	-0.28	0.33	0.515
	Respiratory tract	61	2.3	1.8	3.0	23	1.7	1.1	2.5	0.60	-0.38	1.47	0.212

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	%	**LL**	**UL**	
	infection (10062352)												
	Rhinitis (10039083)	308	11.6	10.4	12.9	163	12.1	10.4	14.0	-0.45	-2.64	1.63	0.676
	Scarlet fever (10039587)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Skin candida (10054152)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Skin infection (10040872)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Tonsillitis (10044008)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Tracheitis (10044302)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Upper respiratory tract infection (10046306)	193	7.3	6.3	8.4	94	7.0	5.7	8.5	0.32	-1.43	1.95	0.711
	Urinary tract infection (10046571)	11	0.4	0.2	0.7	3	0.2	0.0	0.6	0.19	-0.27	0.56	0.329
	Varicella (10046980)	12	0.5	0.2	0.8	11	0.8	0.4	1.5	-0.36	-1.03	0.13	0.152
	Viral infection (10047461)	8	0.3	0.1	0.6	7	0.5	0.2	1.1	-0.22	-0.79	0.18	0.289
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Contusion (10050584)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Drug administration error (10064295)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Excoriation (10049796)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Thermal burn (10053615)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Wound (10052428)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Investigations (10022891)	Body temperature increased (10005911)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Medical observation (10053047)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Metabolism and nutrition disorders (10027433)	Anorexia (10002646)	24	0.9	0.6	1.3	11	0.8	0.4	1.5	0.09	-0.61	0.66	0.770
	Cow's milk intolerance (10011241)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Decreased appetite (10061428)	9	0.3	0.2	0.6	4	0.3	0.1	0.8	0.04	-0.44	0.40	0.820
Musculoskeletal and connective tissue disorders (10028395)	Muscle twitching (10028347)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Myalgia (10028411)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pain in extremity (10033425)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Haemangioma (10018814)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Nervous system	Convulsion (10010904)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	%	**LL**	**UL**	
disorders (10029205)													
	Hyperaesthesia (10020568)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Hypertonia (10020852)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Hypotonia (10021118)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Lethargy (10024264)	17	0.6	0.4	1.0	8	0.6	0.3	1.2	0.05	-0.57	0.54	0.853
	Paralysis (10033799)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Petit mal epilepsy (10034759)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Sleep phase rhythm disturbance (10041003)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Somnolence (10041349)	19	0.7	0.4	1.1	15	1.1	0.6	1.8	-0.39	-1.16	0.20	0.199
	Tremor (10044565)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Psychiatric disorders (10037175)	Agitation (10001497)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Apathy (10002942)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Breath holding (10006322)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Crying (10011469)	219	8.3	7.3	9.4	111	8.2	6.8	9.8	0.04	-1.83	1.80	0.963
	Decreased activity (10011953)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Depressed mood (10012374)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Eating disorder (10014062)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Insomnia (10022437)	10	0.4	0.2	0.7	5	0.4	0.1	0.9	0.01	-0.51	0.39	0.973
	Listless (10024642)	19	0.7	0.4	1.1	13	1.0	0.5	1.6	-0.25	-0.97	0.32	0.409
	Merycism (10027387)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Moaning (10027783)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Restlessness (10038743)	22	0.8	0.5	1.3	20	1.5	0.9	2.3	-0.65	-1.50	0.02	0.056
	Sleep disorder (10040984)	5	0.2	0.1	0.4	2	0.1	0.0	0.5	0.04	-0.36	0.32	0.772
	Tearfulness (10043169)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
Reproductive system and breast disorders (10038604)	Scrotal oedema (10039755)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Testicular torsion (10043356)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Respiratory, thoracic and mediastinal disorders (10038738)	Allergic Cough (10053779)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Asthma (10003553)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Cough (10011224)	136	5.1	4.3	6.1	76	5.6	4.5	7.0	-0.50	-2.07	0.94	0.507
	Dysphonia (10013952)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Dyspnoea (10013968)	4	0.2	0.0	0.4	2	0.1	0.0	0.5	0.00	-0.40	0.27	0.983
	Haemoptysis (10018964)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Infantile asthma (10049585)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Nasal congestion	31	1.2	0.8	1.7	16	1.2	0.7	1.9	-0.02	-0.82	0.65	0.966

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	%	**LL**	**UL**	
	(10028735)												
	Obstructive airways disorder (10061877)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pharyngeal erythema (10057009)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pharyngolaryngeal pain (10034844)	6	0.2	0.1	0.5	1	0.1	0.0	0.4	0.15	-0.20	0.43	0.276
	Pneumonia aspiration (10035669)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Productive Cough (10036790)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Rales (10037833)	4	0.2	0.0	0.4	1	0.1	0.0	0.4	0.08	-0.28	0.33	0.515
	Respiratory disorder (10038683)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Rhinitis allergic (10039085)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Rhinorrhoea (10039101)	22	0.8	0.5	1.3	16	1.2	0.7	1.9	-0.36	-1.14	0.27	0.274
	Sneezing (10041232)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Stridor (10042241)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
	Wheezing (10047924)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
Skin and subcutaneous tissue disorders (10040785)	Acne (10000496)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Dermatitis (10012431)	7	0.3	0.1	0.5	2	0.1	0.0	0.5	0.12	-0.29	0.42	0.464
	Dermatitis allergic (10012434)	5	0.2	0.1	0.4	1	0.1	0.0	0.4	0.11	-0.24	0.38	0.376
	Dermatitis atopic (10012438)	31	1.2	0.8	1.7	11	0.8	0.4	1.5	0.36	-0.36	0.97	0.298
	Dermatitis diaper (10012444)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Dry skin (10013786)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
	Eczema (10014184)	33	1.2	0.9	1.7	12	0.9	0.5	1.5	0.36	-0.39	0.99	0.312
	Erythema (10015150)	4	0.2	0.0	0.4	4	0.3	0.1	0.8	-0.15	-0.62	0.15	0.331
	Generalised erythema (10051576)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Intertrigo (10022622)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Neurodermatitis (10029263)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Photosensitivity reaction (10034972)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pruritus (10037087)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Rash (10037844)	32	1.2	0.8	1.7	15	1.1	0.6	1.8	0.10	-0.70	0.76	0.789
	Rash papular (10037876)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Seborrhoeic dermatitis (10039793)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Skin burning sensation (10054786)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Skin reaction (10040914)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Urticaria (10046735)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	%	**LL**	**UL**	
Social circumstances (10041244)	Ear piercing (10014021)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
Surgical and medical procedures (10042613)	Ear tube insertion (10057900)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Hydrocele repair (10020499)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Prophylaxis (10036898)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Vascular disorders (10047065)	Flushing (10016825)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Haemorrhage (10055798)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pallor (10033546)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

N = number of subjects having received at least one dose of HRV/placebo
n/% = number/percentage of subjects reporting at least one unsolicited adverse event in the specified PT category within 31 days after any HRV/placebo doses
At least one symptom = number of subjects reporting at least one unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA PT
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = result of the comparison between groups of the percentages of subjects reporting the specified unsolicited adverse event within 31 days after any doses, by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 were used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 356 Percentage of doses with unsolicited AEs classified by MedDRA primary SOC from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

	HRV N = 5267				Placebo N = 2686			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	2394	45.5	44.1	46.8	1182	44.0	42.1	45.9
Blood and lymphatic system disorders (10005329)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
Congenital, familial and genetic disorders (10010331)	3	0.1	0.0	0.2	1	0.0	0.0	0.2
Ear and labyrinth disorders (10013993)	4	0.1	0.0	0.2	2	0.1	0.0	0.3
Eye disorders (10015919)	95	1.8	1.5	2.2	51	1.9	1.4	2.5
Gastrointestinal disorders (10017947)	440	8.4	7.6	9.1	204	7.6	6.6	8.7
General disorders and administration site conditions (10018065)	1369	26.0	24.8	27.2	640	23.8	22.2	25.5
Immune system disorders (10021428)	13	0.2	0.1	0.4	5	0.2	0.1	0.4
Infections and infestations (10021881)	931	17.7	16.7	18.7	479	17.8	16.4	19.3
Injury, poisoning and procedural complications (10022117)	4	0.1	0.0	0.2	4	0.1	0.0	0.4
Investigations (10022891)	4	0.1	0.0	0.2	1	0.0	0.0	0.2
Metabolism and nutrition disorders (10027433)	38	0.7	0.5	1.0	15	0.6	0.3	0.9
Musculoskeletal and connective tissue disorders (10028395)	4	0.1	0.0	0.2	0	0.0	0.0	0.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Nervous system disorders (10029205)	49	0.9	0.7	1.2	31	1.2	0.8	1.6
Psychiatric disorders (10037175)	308	5.8	5.2	6.5	158	5.9	5.0	6.8
Reproductive system and breast disorders (10038604)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	208	3.9	3.4	4.5	114	4.2	3.5	5.1
Skin and subcutaneous tissue disorders (10040785)	129	2.4	2.0	2.9	55	2.0	1.5	2.7
Social circumstances (10041244)	1	0.0	0.0	0.1	2	0.1	0.0	0.3
Surgical and medical procedures (10042613)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
Vascular disorders (10047065)	3	0.1	0.0	0.2	0	0.0	0.0	0.1

N = Total number of HRV or Placebo doses administered

n/% = number/percentage of doses followed by at least one unsolicited adverse event in the specified primary SOC category within 31 days after any HRV/placebo doses

At least one symptom = number of doses followed by f at least one unsolicited adverse event within 31 days after any HRV/placebo dose, whatever the MedDRA SOC

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

Supplement 357 Percentage of doses with unsolicited AEs classified by MedDRA primary SOC and PT from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

		HRV N = 5267				Placebo N = 2686			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		2394	45.5	44.1	46.8	1182	44.0	42.1	45.9
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Lymphadenopathy (10025197)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Congenital, familial and genetic disorders (10010331)	Congenital labia pudendi adhesions (10050268)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Hydrocele (10020488)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Laryngomalacia (10060786)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	4	0.1	0.0	0.2	0	0.0	0.0	0.1
	Ear pruritus (10052138)	0	0.0	0.0	0.1	2	0.1	0.0	0.3
Eye disorders (10015919)	Conjunctivitis (10010741)	87	1.7	1.3	2.0	43	1.6	1.2	2.2
	Eye discharge (10015915)	6	0.1	0.0	0.2	6	0.2	0.1	0.5
	Eye inflammation (10015943)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Eyelid oedema (10015993)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Keratitis (10023332)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Strabismus (10042159)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Gastrointestinal disorders (10017947)	Abdominal discomfort (10000059)	2	0.0	0.0	0.1	3	0.1	0.0	0.3
	Abdominal distension (10000060)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Abdominal pain (10000081)	27	0.5	0.3	0.7	7	0.3	0.1	0.5
	Abdominal pain upper (10000087)	40	0.8	0.5	1.0	22	0.8	0.5	1.2
	Abnormal faeces (10000133)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Anal fissure (10002153)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Anorectal disorder (10002644)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Aphthous stomatitis (10002958)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Constipation (10010774)	52	1.0	0.7	1.3	21	0.8	0.5	1.2
	Diarrhea (10012735)	0	0.0	0.0	0.1	2	0.1	0.0	0.3
	Dyspepsia (10013946)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Enterocolitis (10014893)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Flatulence (10016766)	107	2.0	1.7	2.4	36	1.3	0.9	1.9
	Frequent bowel movements (10017367)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Gastrointestinal disorder (10017944)	86	1.6	1.3	2.0	43	1.6	1.2	2.2
	Gastrooesophageal reflux disease (10017885)	6	0.1	0.0	0.2	5	0.2	0.1	0.4
	Haematochezia (10018836)	12	0.2	0.1	0.4	7	0.3	0.1	0.5
	Infantile colic (10021746)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Infantile spitting up (10063338)	14	0.3	0.1	0.4	8	0.3	0.1	0.6

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Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Infrequent bowel movements (10059158)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Inguinal hernia (10022016)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Intussusception (10022863)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Mucous stools (10028140)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Oesophagitis (10030216)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Painful defaecation (10055664)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Perianal erythema (10056273)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rectal haemorrhage (10038063)	0	0.0	0.0	0.1	2	0.1	0.0	0.3
	Regurgitation of food (10038288)	40	0.8	0.5	1.0	14	0.5	0.3	0.9
	Salivary hypersecretion (10039424)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Stomatitis (10042128)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Teething (10043183)	57	1.1	0.8	1.4	26	1.0	0.6	1.4
	Toothache (10044055)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
	Vomiting (10047700)	51	1.0	0.7	1.3	28	1.0	0.7	1.5
General disorders and administration site conditions (10018065)	Application site pain (10003051)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Chills (10008531)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Discomfort (10013082)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Fatigue (10016256)	47	0.9	0.7	1.2	27	1.0	0.7	1.5
	Ill-defined disorder (10061520)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Inflammation (10061218)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Influenza like illness (10022004)	18	0.3	0.2	0.5	6	0.2	0.1	0.5
	Injection site erythema (10022061)	23	0.4	0.3	0.7	10	0.4	0.2	0.7
	Injection site haemorrhage (10022067)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
	Injection site induration (10022075)	14	0.3	0.1	0.4	6	0.2	0.1	0.5
	Injection site inflammation (10022078)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Injection site irritation (10022079)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Injection site mass (10022081)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
	Injection site nodule (10057880)	5	0.1	0.0	0.2	6	0.2	0.1	0.5
	Injection site pain (10022086)	118	2.2	1.9	2.7	44	1.6	1.2	2.2
	Injection site reaction (10022095)	16	0.3	0.2	0.5	8	0.3	0.1	0.6
	Injection site swelling (10053425)	28	0.5	0.4	0.8	15	0.6	0.3	0.9
	Irritability (10022998)	695	13.2	12.3	14.1	283	10.5	9.4	11.8
	Malaise (10025482)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Mucous membrane disorder	1	0.0	0.0	0.1	0	0.0	0.0	0.1

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Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	(10028133)								
	Oedema peripheral (10030124)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pain (10033371)	8	0.2	0.1	0.3	2	0.1	0.0	0.3
	Pyrexia (10037660)	755	14.3	13.4	15.3	383	14.3	13.0	15.6
	Venipuncture site pain (10048823)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Immune system disorders (10021428)	Atopy (10003645)	4	0.1	0.0	0.2	0	0.0	0.0	0.1
	Food allergy (10016946)	2	0.0	0.0	0.1	2	0.1	0.0	0.3
	Hypersensitivity (10020751)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
	Milk allergy (10027633)	5	0.1	0.0	0.2	3	0.1	0.0	0.3
Infections and infestations (10021881)	Abscess (10000269)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Bronchiolitis (10006448)	34	0.6	0.4	0.9	20	0.7	0.5	1.1
	Bronchitis (10006451)	40	0.8	0.5	1.0	23	0.9	0.5	1.3
	Bronchitis acute (10006452)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Bronchopneumonia (10006469)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Campylobacter infection (10051226)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Candida nappy rash (10007135)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Candidiasis (10007152)	11	0.2	0.1	0.4	7	0.3	0.1	0.5
	Ear infection (10014011)	26	0.5	0.3	0.7	12	0.4	0.2	0.8
	Eczema infected (10014199)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Enterovirus infection (10014909)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Exanthema subitum (10015586)	12	0.2	0.1	0.4	11	0.4	0.2	0.7
	Eye infection (10015929)	2	0.0	0.0	0.1	2	0.1	0.0	0.3
	Eyelid infection (10015988)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Gastroenteritis (10017888)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Gastrointestinal infection (10017964)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Genital candidiasis (10018143)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Herpetic gingivostomatitis (10019996)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Impetigo (10021531)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Infection (10021789)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Influenza (10022000)	39	0.7	0.5	1.0	13	0.5	0.3	0.8
	Injection site cellulitis (10050057)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Laryngitis (10023874)	18	0.3	0.2	0.5	7	0.3	0.1	0.5
	Meningitis (10027199)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Nasopharyngitis (10028810)	29	0.6	0.4	0.8	17	0.6	0.4	1.0
	Oral candidiasis (10030963)	11	0.2	0.1	0.4	2	0.1	0.0	0.3
	Oral fungal infection (10061324)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Otitis externa (10033072)	1	0.0	0.0	0.1	2	0.1	0.0	0.3

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	Otitis media (10033078)	131	2.5	2.1	2.9	71	2.6	2.1	3.3
	Otitis media acute (10033079)	5	0.1	0.0	0.2	1	0.0	0.0	0.2
	Paronychia (10034016)	3	0.1	0.0	0.2	1	0.0	0.0	0.2
	Perianal abscess (10034447)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pertussis (10034738)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pharyngitis (10034835)	15	0.3	0.2	0.5	7	0.3	0.1	0.5
	Pneumonia (10035664)	4	0.1	0.0	0.2	2	0.1	0.0	0.3
	Pneumonia respiratory syncytial viral (10035732)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pyelonephritis (10037596)	5	0.1	0.0	0.2	1	0.0	0.0	0.2
	Pyelonephritis acute (10037597)	4	0.1	0.0	0.2	1	0.0	0.0	0.2
	Respiratory tract infection (10062352)	63	1.2	0.9	1.5	25	0.9	0.6	1.4
	Rhinitis (10039083)	345	6.6	5.9	7.3	179	6.7	5.8	7.7
	Scarlet fever (10039587)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Skin candida (10054152)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Skin infection (10040872)	1	0.0	0.0	0.1	2	0.1	0.0	0.3
	Tonsillitis (10044008)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Tracheitis (10044302)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Upper respiratory tract infection (10046306)	203	3.9	3.4	4.4	104	3.9	3.2	4.7
	Urinary tract infection (10046571)	11	0.2	0.1	0.4	4	0.1	0.0	0.4
	Varicella (10046980)	12	0.2	0.1	0.4	11	0.4	0.2	0.7
	Viral infection (10047461)	8	0.2	0.1	0.3	8	0.3	0.1	0.6
Injury, poisoning and procedural complications (10022117)	Concussion (10010254)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Contusion (10050584)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Drug administration error (10064295)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Excoriation (10049796)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Thermal burn (10053615)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
	Wound (10052428)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Investigations (10022891)	Body temperature increased (10005911)	3	0.1	0.0	0.2	1	0.0	0.0	0.2
	Medical observation (10053047)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Metabolism and nutrition disorders (10027433)	Anorexia (10002646)	27	0.5	0.3	0.7	11	0.4	0.2	0.7
	Cow's milk intolerance (10011241)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Decreased appetite (10061428)	10	0.2	0.1	0.3	4	0.1	0.0	0.4
Musculoskeletal and connective tissue disorders (10028395)	Muscle twitching (10028347)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Myalgia (10028411)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pain in extremity (10033425)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
Neoplasms benign, malignant and	Haemangioma (10018814)	0	0.0	0.0	0.1	1	0.0	0.0	0.2

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unspecified (incl cysts and polyps) (10029104)									
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Hyperaesthesia (10020568)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Hypertonia (10020852)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Hypotonia (10021118)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Lethargy (10024264)	20	0.4	0.2	0.6	8	0.3	0.1	0.6
	Paralysis (10033799)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Petit mal epilepsy (10034759)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Sleep phase rhythm disturbance (10041003)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Somnolence (10041349)	25	0.5	0.3	0.7	18	0.7	0.4	1.1
	Tremor (10044565)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Psychiatric disorders (10037175)	Agitation (10001497)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Apathy (10002942)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Breath holding (10006322)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Crying (10011469)	256	4.9	4.3	5.5	126	4.7	3.9	5.6
	Decreased activity (10011953)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Depressed mood (10012374)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Eating disorder (10014062)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Insomnia (10022437)	10	0.2	0.1	0.3	5	0.2	0.1	0.4
	Listless (10024642)	21	0.4	0.2	0.6	13	0.5	0.3	0.8
	Merycism (10027387)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Moaning (10027783)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Restlessness (10038743)	23	0.4	0.3	0.7	20	0.7	0.5	1.1
	Sleep disorder (10040984)	5	0.1	0.0	0.2	2	0.1	0.0	0.3
	Tearfulness (10043169)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
Reproductive system and breast disorders (10038604)	Scrotal oedema (10039755)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Testicular torsion (10043356)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	Allergic Cough (10053779)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Asthma (10003553)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Cough (10011224)	140	2.7	2.2	3.1	79	2.9	2.3	3.7
	Dysphonia (10013952)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Dyspnoea (10013968)	5	0.1	0.0	0.2	2	0.1	0.0	0.3
	Haemoptysis (10018964)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Infantile asthma (10049585)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Nasal congestion (10028735)	32	0.6	0.4	0.9	18	0.7	0.4	1.1
	Obstructive airways disorder (10061877)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pharyngeal erythema (10057009)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pharyngolaryngeal pain (10034844)	6	0.1	0.0	0.2	1	0.0	0.0	0.2

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	Pneumonia aspiration (10035669)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Productive Cough (10036790)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rales (10037833)	4	0.1	0.0	0.2	1	0.0	0.0	0.2
	Respiratory disorder (10038683)	2	0.0	0.0	0.1	2	0.1	0.0	0.3
	Rhinitis allergic (10039085)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rhinorrhoea (10039101)	23	0.4	0.3	0.7	18	0.7	0.4	1.1
	Sneezing (10041232)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Stridor (10042241)	0	0.0	0.0	0.1	2	0.1	0.0	0.3
	Wheezing (10047924)	4	0.1	0.0	0.2	0	0.0	0.0	0.1
Skin and subcutaneous tissue disorders (10040785)	Acne (10000496)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Dermatitis (10012431)	7	0.1	0.1	0.3	2	0.1	0.0	0.3
	Dermatitis allergic (10012434)	6	0.1	0.0	0.2	1	0.0	0.0	0.2
	Dermatitis atopic (10012438)	32	0.6	0.4	0.9	11	0.4	0.2	0.7
	Dermatitis diaper (10012444)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
	Dry skin (10013786)	4	0.1	0.0	0.2	0	0.0	0.0	0.1
	Eczema (10014184)	34	0.6	0.4	0.9	12	0.4	0.2	0.8
	Erythema (10015150)	4	0.1	0.0	0.2	6	0.2	0.1	0.5
	Generalised erythema (10051576)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Intertrigo (10022622)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Neurodermatitis (10029263)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Photosensitivity reaction (10034972)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pruritus (10037087)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Rash (10037844)	32	0.6	0.4	0.9	15	0.6	0.3	0.9
	Rash papular (10037876)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Seborrhoeic dermatitis (10039793)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Skin burning sensation (10054786)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Skin reaction (10040914)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Urticaria (10046735)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
Social circumstances (10041244)	Ear piercing (10014021)	1	0.0	0.0	0.1	2	0.1	0.0	0.3
Surgical and medical procedures (10042613)	Ear tube insertion (10057900)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Hydrocele repair (10020499)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Prophylaxis (10036898)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Vascular disorders (10047065)	Flushing (10016825)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Haemorrhage (10055798)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pallor (10033546)	1	0.0	0.0	0.1	0	0.0	0.0	0.1

N = Total number of HRV or Placebo doses administered

n/% = number/percentage of doses followed by at least one unsolicited adverse event in the specified PT category within 31 days after any HRV/placebo doses

At least one symptom = number of doses followed by at least one unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA PT

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

Supplement 358 Percentage of subjects with grade 3 unsolicited AEs classified by MedDRA primary SOC from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

	HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	
At least one symptom	233	8.8	7.8	10.0	118	8.8	7.3	10.4	0.05	-1.87	1.86	0.956
Ear and labyrinth disorders (10013993)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
Eye disorders (10015919)	11	0.4	0.2	0.7	4	0.3	0.1	0.8	0.12	-0.37	0.50	0.561
Gastrointestinal disorders (10017947)	19	0.7	0.4	1.1	13	1.0	0.5	1.6	-0.25	-0.97	0.32	0.409
General disorders and administration site conditions (10018065)	82	3.1	2.5	3.8	50	3.7	2.8	4.9	-0.61	-1.90	0.54	0.308
Immune system disorders (10021428)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
Infections and infestations (10021881)	150	5.7	4.8	6.6	73	5.4	4.3	6.8	0.25	-1.31	1.70	0.741
Injury, poisoning and procedural complications (10022117)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Metabolism and nutrition disorders (10027433)	5	0.2	0.1	0.4	3	0.2	0.0	0.6	-0.03	-0.48	0.26	0.822
Musculoskeletal and connective tissue disorders (10028395)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
Psychiatric disorders (10037175)	17	0.6	0.4	1.0	7	0.5	0.2	1.1	0.12	-0.47	0.60	0.634
Reproductive system and breast disorders (10038604)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Respiratory, thoracic and mediastinal disorders (10038738)	27	1.0	0.7	1.5	20	1.5	0.9	2.3	-0.46	-1.32	0.23	0.199
Skin and subcutaneous tissue disorders (10040785)	6	0.2	0.1	0.5	2	0.1	0.0	0.5	0.08	-0.33	0.37	0.600
Surgical and medical procedures (10042613)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

N = number of subjects having received at least one dose of HRV/placebo

n/% = number/percentage of subjects reporting at least one grade 3 unsolicited adverse event in the specified primary SOC category within 31 days after any HRV/placebo doses

At least one symptom = number of subjects reporting at least one grade 3 unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA SOC

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit

P-value = result of the comparison between groups of the percentages of subjects reporting the specified grade 3 unsolicited adverse event within 31 days after any doses , by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 were used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 359 Percentage of subjects with grade 3 unsolicited AEs classified by MedDRA primary SOC and PT from Day 0 to Day 30 after any HRV/placebo doses – Pooled countries – Total vaccinated cohort

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
At least one symptom		233	8.8	7.8	10.0	118	8.8	7.3	10.4	0.05	-1.87	1.86	0.956
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
Eye disorders (10015919)	Conjunctivitis (10010741)	11	0.4	0.2	0.7	4	0.3	0.1	0.8	0.12	-0.37	0.50	0.561
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Abdominal pain upper (10000087)	3	0.1	0.0	0.3	1	0.1	0.0	0.4	0.04	-0.31	0.27	0.711
	Constipation (10010774)	4	0.2	0.0	0.4	1	0.1	0.0	0.4	0.08	-0.28	0.33	0.515
	Flatulence (10016766)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Gastrooesophageal reflux disease (10017885)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Infantile spitting up (10063338)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Inguinal hernia (10022016)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Oesophagitis (10030216)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Painful defaecation (10055664)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Regurgitation of food (10038288)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Teething (10043183)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Vomiting (10047700)	5	0.2	0.1	0.4	2	0.1	0.0	0.5	0.04	-0.36	0.32	0.772
General disorders and administration site conditions (10018065)	Discomfort (10013082)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Fatigue (10016256)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Influenza like illness (10022004)	3	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.11	-0.55	0.15	0.400
	Injection site erythema (10022061)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Injection site induration (10022075)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Injection site pain (10022086)	3	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.11	-0.55	0.15	0.400
	Injection site swelling (10053425)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Irritability (10022998)	26	1.0	0.6	1.4	13	1.0	0.5	1.6	0.02	-0.73	0.63	0.956
	Malaise (10025482)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Pain (10033371)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Pyrexia (10037660)	61	2.3	1.8	3.0	35	2.6	1.8	3.6	-0.29	-1.40	0.68	0.570
Immune system disorders (10021428)	Atopy (10003645)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Hypersensitivity	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
	(10020751)												
Infections and infestations (10021881)	Bronchiolitis (10006448)	4	0.2	0.0	0.4	8	0.6	0.3	1.2	-0.44	-1.03	-0.08	0.016
	Bronchitis (10006451)	8	0.3	0.1	0.6	3	0.2	0.0	0.6	0.08	-0.37	0.41	0.649
	Candidiasis (10007152)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Ear infection (10014011)	12	0.5	0.2	0.8	6	0.4	0.2	1.0	0.01	-0.55	0.43	0.970
	Exanthema subitum (10015586)	2	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.15	-0.58	0.09	0.214
	Eye infection (10015929)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Influenza (10022000)	4	0.2	0.0	0.4	4	0.3	0.1	0.8	-0.15	-0.62	0.15	0.331
	Laryngitis (10023874)	9	0.3	0.2	0.6	2	0.1	0.0	0.5	0.19	-0.22	0.52	0.274
	Meningitis (10027199)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Otitis externa (10033072)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	0.047
	Otitis media (10033078)	60	2.3	1.7	2.9	32	2.4	1.6	3.3	-0.11	-1.19	0.84	0.832
	Otitis media acute (10033079)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pharyngitis (10034835)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Pneumonia (10035664)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Pyelonephritis (10037596)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Pyelonephritis acute (10037597)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Respiratory tract infection (10062352)	8	0.3	0.1	0.6	2	0.1	0.0	0.5	0.15	-0.26	0.47	0.357
	Rhinitis (10039083)	18	0.7	0.4	1.1	6	0.4	0.2	1.0	0.24	-0.34	0.70	0.363
	Tonsillitis (10044008)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Upper respiratory tract infection (10046306)	42	1.6	1.1	2.1	16	1.2	0.7	1.9	0.40	-0.43	1.12	0.317
	Urinary tract infection (10046571)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Varicella (10046980)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Viral infection (10047461)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Injury, poisoning and procedural complications (10022117)	Thermal burn (10053615)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Metabolism and nutrition disorders (10027433)	Anorexia (10002646)	2	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.15	-0.58	0.09	0.214
	Decreased appetite (10061428)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
Musculoskeletal and connective tissue disorders (10028395)	Muscle twitching (10028347)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Myalgia (10028411)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pain in extremity (10033425)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Psychiatric disorders (10037175)	Crying (10011469)	16	0.6	0.3	1.0	7	0.5	0.2	1.1	0.09	-0.51	0.55	0.736
	Restlessness (10038743)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Sleep disorder (10040984)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
Reproductive system and breast disorders (10038604)	Testicular torsion (10043356)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	22	0.8	0.5	1.3	16	1.2	0.7	1.9	-0.36	-1.14	0.27	0.274
	Dyspnoea (10013968)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Nasal congestion (10028735)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Pharyngolaryngeal pain (10034844)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Productive Cough (10036790)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Rales (10037833)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Respiratory disorder (10038683)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Rhinorrhoea (10039101)	0	0.0	0.0	0.1	6	0.4	0.2	1.0	-0.45	-0.97	-0.20	0.001
	Stridor (10042241)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Wheezing (10047924)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Skin and subcutaneous tissue disorders (10040785)	Dermatitis (10012431)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Dermatitis atopic (10012438)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Eczema (10014184)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Rash (10037844)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
Surgical and medical procedures (10042613)	Ear tube insertion (10057900)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

N = number of subjects having received at least one dose of HRV/placebo
n/% = number/percentage of subjects reporting at least one grade 3 unsolicited adverse event in the specified PT category within 31 days after any HRV/placebo doses
At least one symptom = number of subjects reporting at least one grade 3 unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA PT
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = result of the comparison between groups of the percentages of subjects reporting the specified grade 3 unsolicited adverse event within 31 days after any doses , by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 were used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 360 Percentage of doses with grade 3 unsolicited AEs classified by MedDRA primary SOC from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

	HRV N = 5267				Placebo N = 2686			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	250	4.7	4.2	5.4	131	4.9	4.1	5.8
Ear and labyrinth disorders (10013993)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
Eye disorders (10015919)	11	0.2	0.1	0.4	4	0.1	0.0	0.4
Gastrointestinal disorders (10017947)	20	0.4	0.2	0.6	13	0.5	0.3	0.8
General disorders and administration site conditions (10018065)	83	1.6	1.3	1.9	52	1.9	1.4	2.5
Immune system disorders (10021428)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
Infections and infestations (10021881)	153	2.9	2.5	3.4	78	2.9	2.3	3.6
Injury, poisoning and procedural complications (10022117)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Metabolism and nutrition disorders (10027433)	5	0.1	0.0	0.2	3	0.1	0.0	0.3
Musculoskeletal and connective tissue disorders (10028395)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
Psychiatric disorders (10037175)	17	0.3	0.2	0.5	7	0.3	0.1	0.5
Reproductive system and breast disorders (10038604)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	28	0.5	0.4	0.8	20	0.7	0.5	1.1
Skin and subcutaneous tissue disorders (10040785)	6	0.1	0.0	0.2	2	0.1	0.0	0.3
Surgical and medical procedures (10042613)	1	0.0	0.0	0.1	0	0.0	0.0	0.1

N = Total number of HRV or Placebo doses administered

n/% = number/percentage of doses followed by at least one grade 3 unsolicited adverse event in the specified primary SOC category within 31 days after any HRV/placebo doses

At least one symptom = number of doses followed by at least one grade 3 unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA SOC

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

Supplement 361 Percentage of doses with grade 3 unsolicited AEs classified by MedDRA primary SOC and PT from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

		HRV N = 5267				Placebo N = 2686			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		250	4.7	4.2	5.4	131	4.9	4.1	5.8
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
Eye disorders (10015919)	Conjunctivitis (10010741)	11	0.2	0.1	0.4	4	0.1	0.0	0.4
Gastrointestinal disorders (10017947)	Abdominal pain (10000081)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Abdominal pain upper (10000087)	3	0.1	0.0	0.2	1	0.0	0.0	0.2
	Constipation (10010774)	4	0.1	0.0	0.2	1	0.0	0.0	0.2
	Flatulence (10016766)	2	0.0	0.0	0.1	2	0.1	0.0	0.3
	Gastrooesophageal reflux disease (10017885)	2	0.0	0.0	0.1	2	0.1	0.0	0.3
	Infantile spitting up (10063338)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Inguinal hernia (10022016)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Oesophagitis (10030216)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Painful defaecation (10055664)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Regurgitation of food (10038288)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Teething (10043183)	1	0.0	0.0	0.1	2	0.1	0.0	0.3
	Vomiting (10047700)	5	0.1	0.0	0.2	2	0.1	0.0	0.3
General disorders and administration site conditions (10018065)	Discomfort (10013082)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Fatigue (10016256)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Influenza like illness (10022004)	3	0.1	0.0	0.2	3	0.1	0.0	0.3
	Injection site erythema (10022061)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Injection site induration (10022075)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Injection site pain (10022086)	3	0.1	0.0	0.2	3	0.1	0.0	0.3
	Injection site swelling (10053425)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Irritability (10022998)	26	0.5	0.3	0.7	15	0.6	0.3	0.9
	Malaise (10025482)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pain (10033371)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pyrexia (10037660)	62	1.2	0.9	1.5	35	1.3	0.9	1.8
Immune system disorders (10021428)	Atopy (10003645)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Hypersensitivity (10020751)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Infections and infestations (10021881)	Bronchiolitis (10006448)	4	0.1	0.0	0.2	8	0.3	0.1	0.6
	Bronchitis (10006451)	8	0.2	0.1	0.3	3	0.1	0.0	0.3

		HRV N = 5267				Placebo N = 2686			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Candidiasis (10007152)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Ear infection (10014011)	12	0.2	0.1	0.4	6	0.2	0.1	0.5
	Exanthema subitum (10015586)	2	0.0	0.0	0.1	3	0.1	0.0	0.3
	Eye infection (10015929)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Influenza (10022000)	4	0.1	0.0	0.2	4	0.1	0.0	0.4
	Laryngitis (10023874)	9	0.2	0.1	0.3	2	0.1	0.0	0.3
	Meningitis (10027199)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Otitis externa (10033072)	0	0.0	0.0	0.1	2	0.1	0.0	0.3
	Otitis media (10033078)	60	1.1	0.9	1.5	32	1.2	0.8	1.7
	Otitis media acute (10033079)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pharyngitis (10034835)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pneumonia (10035664)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pyelonephritis (10037596)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pyelonephritis acute (10037597)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Respiratory tract infection (10062352)	8	0.2	0.1	0.3	3	0.1	0.0	0.3
	Rhinitis (10039083)	18	0.3	0.2	0.5	6	0.2	0.1	0.5
	Tonsillitis (10044008)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Upper respiratory tract infection (10046306)	43	0.8	0.6	1.1	16	0.6	0.3	1.0
	Urinary tract infection (10046571)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Varicella (10046980)	1	0.0	0.0	0.1	2	0.1	0.0	0.3
	Viral infection (10047461)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Injury, poisoning and procedural complications (10022117)	Thermal burn (10053615)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Metabolism and nutrition disorders (10027433)	Anorexia (10002646)	2	0.0	0.0	0.1	3	0.1	0.0	0.3
	Decreased appetite (10061428)	3	0.1	0.0	0.2	0	0.0	0.0	0.1
Musculoskeletal and connective tissue disorders (10028395)	Muscle twitching (10028347)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Myalgia (10028411)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Pain in extremity (10033425)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Psychiatric disorders (10037175)	Crying (10011469)	16	0.3	0.2	0.5	7	0.3	0.1	0.5
	Restlessness (10038743)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Sleep disorder (10040984)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Reproductive system and breast disorders (10038604)	Testicular torsion (10043356)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	23	0.4	0.3	0.7	16	0.6	0.3	1.0
	Dyspnoea (10013968)	2	0.0	0.0	0.1	1	0.0	0.0	0.2

		HRV N = 5267				Placebo N = 2686			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Nasal congestion (10028735)	1	0.0	0.0	0.1	2	0.1	0.0	0.3
	Pharyngolaryngeal pain (10034844)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Productive Cough (10036790)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rales (10037833)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Respiratory disorder (10038683)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Rhinorrhoea (10039101)	0	0.0	0.0	0.1	6	0.2	0.1	0.5
	Stridor (10042241)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Wheezing (10047924)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis (10012431)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Dermatitis atopic (10012438)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Eczema (10014184)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rash (10037844)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
Surgical and medical procedures (10042613)	Ear tube insertion (10057900)	1	0.0	0.0	0.1	0	0.0	0.0	0.1

N = Total number of HRV or Placebo doses administered

n/% = number/percentage of doses followed by at least one grade 3 unsolicited adverse event in the specified PT category within 31 days after any HRV/placebo doses

At least one symptom = number of doses followed by at least one grade 3 unsolicited adverse event within 31 days after any HRV/placebo doses, whatever the MedDRA PT

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

Supplement 362 Percentage of subjects with unsolicited AES assessed as causally related to vaccination classified by MedDRA primary SOC from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

	HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	
At least one symptom	772	29.2	27.4	30.9	373	27.7	25.3	30.1	1.51	-1.48	4.42	0.320
Eye disorders (10015919)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Gastrointestinal disorders (10017947)	196	7.4	6.4	8.5	87	6.5	5.2	7.9	0.95	-0.76	2.56	0.267
General disorders and administration site conditions (10018065)	598	22.6	21.0	24.2	270	20.0	17.9	22.3	2.57	-0.14	5.20	0.063
Immune system disorders (10021428)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Infections and infestations (10021881)	15	0.6	0.3	0.9	5	0.4	0.1	0.9	0.20	-0.34	0.63	0.407
Investigations (10022891)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
Metabolism and nutrition disorders (10027433)	22	0.8	0.5	1.3	9	0.7	0.3	1.3	0.16	-0.49	0.70	0.577
Musculoskeletal and connective tissue disorders (10028395)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Nervous system disorders (10029205)	21	0.8	0.5	1.2	11	0.8	0.4	1.5	-0.02	-0.72	0.53	0.940
Psychiatric disorders (10037175)	151	5.7	4.9	6.7	86	6.4	5.1	7.8	-0.67	-2.32	0.85	0.395
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.3	4	0.3	0.1	0.8	-0.22	-0.69	0.03	0.088
Skin and subcutaneous tissue disorders (10040785)	3	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.11	-0.55	0.15	0.400
Vascular disorders (10047065)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

N = number of subjects having received at least one dose of HRV/placebo
n/% = number/percentage of subjects reporting at least one unsolicited adverse event assessed as causally related to the vaccination in the specified primary SOC category within 31 days after any HRV/placebo doses
At least one symptom = number of subjects reporting at least one unsolicited adverse event assessed as causally related to the vaccination within 31 days after any HRV/placebo doses, whatever the MedDRA SOC
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = result of the comparison between groups of the percentages of subjects reporting the specified unsolicited adverse event assessed as causally related to the vaccination within 31 days after any doses, by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 were used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 363 Percentage of subjects with unsolicited AEs assessed as causally related to vaccination classified by MedDRA primary SOC and PT from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
At least one symptom		772	29.2	27.4	30.9	373	27.7	25.3	30.1	1.51	-1.48	4.42	0.320
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Gastrointestinal disorders (10017947)	Abdominal discomfort (10000059)	2	0.1	0.0	0.3	3	0.2	0.0	0.6	-0.15	-0.58	0.09	0.214
	Abdominal distension (10000060)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Abdominal pain (10000081)	19	0.7	0.4	1.1	4	0.3	0.1	0.8	0.42	-0.10	0.87	0.096
	Abdominal pain upper (10000087)	32	1.2	0.8	1.7	12	0.9	0.5	1.5	0.32	-0.42	0.95	0.361
	Abnormal faeces (10000133)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Aphthous stomatitis (10002958)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Constipation (10010774)	11	0.4	0.2	0.7	7	0.5	0.2	1.1	-0.10	-0.68	0.32	0.644
	Diarrhea (10012735)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Dyspepsia (10013946)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Flatulence (10016766)	51	1.9	1.4	2.5	20	1.5	0.9	2.3	0.44	-0.47	1.24	0.316
	Frequent bowel movements (10017367)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Gastrointestinal disorder (10017944)	58	2.2	1.7	2.8	30	2.2	1.5	3.2	-0.03	-1.09	0.89	0.946
	Haematochezia (10018836)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Infantile colic (10021746)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Infantile spitting up (10063338)	8	0.3	0.1	0.6	6	0.4	0.2	1.0	-0.14	-0.69	0.24	0.470
	Infrequent bowel movements (10059158)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Intussusception (10022863)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Mucous stools (10028140)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Regurgitation of food (10038288)	25	0.9	0.6	1.4	11	0.8	0.4	1.5	0.13	-0.57	0.71	0.684
	Salivary hypersecretion (10039424)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Vomiting (10047700)	20	0.8	0.5	1.2	10	0.7	0.4	1.4	0.01	-0.66	0.55	0.961
General disorders and administration site	Chills (10008531)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
conditions (10018065)													
	Fatigue (10016256)	36	1.4	1.0	1.9	15	1.1	0.6	1.8	0.25	-0.55	0.93	0.510
	Ill-defined disorder (10061520)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Irritability (10022998)	373	14.1	12.8	15.5	147	10.9	9.3	12.7	3.19	1.01	5.28	0.005
	Malaise (10025482)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Pyrexia (10037660)	355	13.4	12.1	14.8	174	12.9	11.2	14.8	0.51	-1.76	2.67	0.654
Immune system disorders (10021428)	Hypersensitivity (10020751)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Infections and infestations (10021881)	Bronchiolitis (10006448)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Bronchitis (10006451)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Candidiasis (10007152)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Gastroenteritis (10017888)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Influenza (10022000)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Respiratory tract infection (10062352)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Rhinitis (10039083)	4	0.2	0.0	0.4	2	0.1	0.0	0.5	0.00	-0.40	0.27	0.983
	Upper respiratory tract infection (10046306)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
Investigations (10022891)	Body temperature increased (10005911)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
Metabolism and nutrition disorders (10027433)	Anorexia (10002646)	17	0.6	0.4	1.0	7	0.5	0.2	1.1	0.12	-0.47	0.60	0.634
	Decreased appetite (10061428)	6	0.2	0.1	0.5	2	0.1	0.0	0.5	0.08	-0.33	0.37	0.600
Musculoskeletal and connective tissue disorders (10028395)	Muscle twitching (10028347)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Nervous system disorders (10029205)	Lethargy (10024264)	13	0.5	0.3	0.8	2	0.1	0.0	0.5	0.34	-0.08	0.72	0.094
	Sleep phase rhythm disturbance (10041003)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Somnolence (10041349)	8	0.3	0.1	0.6	8	0.6	0.3	1.2	-0.29	-0.89	0.12	0.168
Psychiatric disorders (10037175)	Apathy (10002942)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Crying (10011469)	129	4.9	4.1	5.8	69	5.1	4.0	6.4	-0.24	-1.75	1.14	0.738
	Decreased activity (10011953)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Insomnia (10022437)	4	0.2	0.0	0.4	3	0.2	0.0	0.6	-0.07	-0.51	0.21	0.610
	Listless (10024642)	10	0.4	0.2	0.7	10	0.7	0.4	1.4	-0.36	-1.01	0.09	0.123
	Moaning (10027783)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Restlessness (10038743)	13	0.5	0.3	0.8	13	1.0	0.5	1.6	-0.47	-1.18	0.05	0.079
	Sleep disorder (10040984)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
Respiratory, thoracic	Cough (10011224)	1	0.0	0.0	0.2	3	0.2	0.0	0.6	-0.18	-0.62	0.03	0.081

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			P-Value
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	
and mediastinal disorders (10038738)													
	Nasal congestion (10028735)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Pharyngolaryngeal pain (10034844)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Rales (10037833)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Erythema (10015150)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Rash (10037844)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Skin reaction (10040914)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Vascular disorders (10047065)	Pallor (10033546)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

N = number of subjects having received at least one dose of HRV/placebo
n/% = number/percentage of subjects reporting at least one unsolicited adverse event assessed as causally related to the vaccination in the specified PT category within 31 days after any HRV/placebo doses
At least one symptom = number of subjects reporting at least one unsolicited adverse event assessed as causally related to the vaccination within 31 days after any HRV/placebo doses, whatever the MedDRA PT
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI* = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = result of the comparison between groups of the percentages of subjects reporting the specified unsolicited adverse event assessed as causally related to the vaccination within 31 days after any doses, by a two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 were used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 364 Percentage of doses with unsolicited AEs assessed as causally related to vaccination classified by MedDRA primary SOC from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

	HRV N = 5267				Placebo N = 2686			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	1039	19.7	18.7	20.8	479	17.8	16.4	19.3
Eye disorders (10015919)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Gastrointestinal disorders (10017947)	226	4.3	3.8	4.9	103	3.8	3.1	4.6
General disorders and administration site conditions (10018065)	786	14.9	14.0	15.9	346	12.9	11.6	14.2
Immune system disorders (10021428)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Infections and infestations (10021881)	15	0.3	0.2	0.5	5	0.2	0.1	0.4
Investigations (10022891)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
Metabolism and nutrition disorders (10027433)	26	0.5	0.3	0.7	9	0.3	0.2	0.6
Musculoskeletal and connective tissue disorders (10028395)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Nervous system disorders (10029205)	27	0.5	0.3	0.7	12	0.4	0.2	0.8
Psychiatric disorders (10037175)	177	3.4	2.9	3.9	94	3.5	2.8	4.3
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.0	0.0	0.1	4	0.1	0.0	0.4
Skin and subcutaneous tissue disorders (10040785)	3	0.1	0.0	0.2	4	0.1	0.0	0.4
Vascular disorders (10047065)	1	0.0	0.0	0.1	0	0.0	0.0	0.1

N = Total number of HRV or Placebo doses administered

n/% = number/percentage of doses followed by at least one unsolicited adverse event assessed as causally related to the vaccination in the specified primary SOC category within 31 days after any HRV/placebo doses

At least one symptom = number of doses followed by at least one unsolicited adverse event assessed as causally related to the vaccination within 31 days after any HRV/placebo doses, whatever the MedDRA SOC

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

Supplement 365 Percentage of doses with unsolicited AEs assessed as causally related to vaccination classified by MedDRA primary SOC and PT from Day 0 to Day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

		HRV N = 5267				Placebo N = 2686			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		1039	19.7	18.7	20.8	479	17.8	16.4	19.3
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Gastrointestinal disorders (10017947)	Abdominal discomfort (10000059)	2	0.0	0.0	0.1	3	0.1	0.0	0.3
	Abdominal distension (10000060)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Abdominal pain (10000081)	21	0.4	0.2	0.6	5	0.2	0.1	0.4
	Abdominal pain upper (10000087)	34	0.6	0.4	0.9	14	0.5	0.3	0.9
	Abnormal faeces (10000133)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Aphthous stomatitis (10002958)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Constipation (10010774)	11	0.2	0.1	0.4	7	0.3	0.1	0.5
	Diarrhea (10012735)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Dyspepsia (10013946)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Flatulence (10016766)	57	1.1	0.8	1.4	22	0.8	0.5	1.2
	Frequent bowel movements (10017367)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Gastrointestinal disorder (10017944)	65	1.2	1.0	1.6	34	1.3	0.9	1.8
	Haematochezia (10018836)	2	0.0	0.0	0.1	2	0.1	0.0	0.3
	Infantile colic (10021746)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Infantile spitting up (10063338)	10	0.2	0.1	0.3	6	0.2	0.1	0.5
	Infrequent bowel movements (10059158)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Intussusception (10022863)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Mucous stools (10028140)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Regurgitation of food (10038288)	30	0.6	0.4	0.8	11	0.4	0.2	0.7
	Salivary hypersecretion (10039424)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Vomiting (10047700)	21	0.4	0.2	0.6	10	0.4	0.2	0.7
General disorders and administration site conditions (10018065)	Chills (10008531)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Fatigue (10016256)	38	0.7	0.5	1.0	16	0.6	0.3	1.0
	Ill-defined disorder (10061520)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Irritability (10022998)	461	8.8	8.0	9.5	179	6.7	5.8	7.7
	Malaise (10025482)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pyrexia (10037660)	438	8.3	7.6	9.1	208	7.7	6.8	8.8
Immune system disorders (10021428)	Hypersensitivity (10020751)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Infections and infestations (10021881)	Bronchiolitis (10006448)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Bronchitis (10006451)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
	Candidiasis (10007152)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Gastroenteritis (10017888)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Influenza (10022000)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Respiratory tract infection (10062352)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rhinitis (10039083)	4	0.1	0.0	0.2	2	0.1	0.0	0.3
	Upper respiratory tract infection (10046306)	2	0.0	0.0	0.1	0	0.0	0.0	0.1
Investigations (10022891)	Body temperature increased (10005911)	2	0.0	0.0	0.1	1	0.0	0.0	0.2
Metabolism and nutrition disorders (10027433)	Anorexia (10002646)	19	0.4	0.2	0.6	7	0.3	0.1	0.5

		HRV N = 5267				Placebo N = 2686			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Decreased appetite (10061428)	7	0.1	0.1	0.3	2	0.1	0.0	0.3
Musculoskeletal and connective tissue disorders (10028395)	Muscle twitching (10028347)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Nervous system disorders (10029205)	Lethargy (10024264)	15	0.3	0.2	0.5	2	0.1	0.0	0.3
	Sleep phase rhythm disturbance (10041003)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Somnolence (10041349)	12	0.2	0.1	0.4	9	0.3	0.2	0.6
Psychiatric disorders (10037175)	Apathy (10002942)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Crying (10011469)	150	2.8	2.4	3.3	76	2.8	2.2	3.5
	Decreased activity (10011953)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Insomnia (10022437)	4	0.1	0.0	0.2	3	0.1	0.0	0.3
	Listless (10024642)	12	0.2	0.1	0.4	10	0.4	0.2	0.7
	Moaning (10027783)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Restlessness (10038743)	14	0.3	0.1	0.4	13	0.5	0.3	0.8
	Sleep disorder (10040984)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	1	0.0	0.0	0.1	3	0.1	0.0	0.3
	Nasal congestion (10028735)	0	0.0	0.0	0.1	1	0.0	0.0	0.2
	Pharyngolaryngeal pain (10034844)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
	Rales (10037833)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Erythema (10015150)	0	0.0	0.0	0.1	2	0.1	0.0	0.3
	Rash (10037844)	1	0.0	0.0	0.1	1	0.0	0.0	0.2
	Skin reaction (10040914)	1	0.0	0.0	0.1	0	0.0	0.0	0.1
Vascular disorders (10047065)	Pallor (10033546)	1	0.0	0.0	0.1	0	0.0	0.0	0.1

N = Total number of HRV or Placebo doses administered

n/% = number/percentage of doses followed by at least one unsolicited adverse event assessed as causally related to the vaccination in the specified PT category within 31 days after any HRV/placebo doses

At least one symptom = number of doses followed by at least one unsolicited adverse event assessed as causally related to the vaccination within 31 days after any HRV/placebo doses, whatever the MedDRA PT

95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit

Supplement 366 SAEs leading to drop-out at Visit 5 – Total vaccinated cohort

PID	Case ID	Symptom (verbatim)	MedDRA PT (code)	Timing (dose/day)	Rel	Start date	End date	Outcome
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.								

PID = subject number
* denotes the SAE reported as the reason for the drop-out
Rel = relationship to vaccination
No = not assessed as causally related to vaccination
Start = start date of the SAE episode
End = end date of the SAE episode

Supplement 367 Non-serious AEs leading to drop-out at Visit 5 – Total vaccinated cohort

PID	Symptom (verbatim)	MedDRA PT (code)	Timing (dose/day)	Rel	Start date	End date	Outcome

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.

Appendix 1
Serious Adverse Events

Appendix 1A
Serious Adverse Events
Case Narratives

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****.*

Appendix 1B
Serious Adverse Events
Summary Table

Appendix 2
Study Information

Protocol Amendment 1

GlaxoSmithKline Biologicals
Rue de l'Institut 89
B-1330 Rixensart Belgium

Study vaccine(s)	GSK Biologicals' live attenuated oral human rotavirus (HRV) vaccine.
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	[redacted] Director
	[redacted] Biostatistician
	[redacted] ***Clinical Development Manager*** **(Amendment 1: 07 June 2005)**
	[redacted] Central Study Coordinator

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Sponsor signatory:	
	[redacted] ***Director*** **(Amendment 1: 07 June 2005)**

Investigator Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine) and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: _____

Investigator Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine) and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: _____

[For Germany only]

"**Leiter der klinischen Prüfung" (LKP) name:** _____

Synopsis

Title A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Indication/Study population Two-dose immunization according to 0, 1 or 2-month schedule against rotavirus disease in healthy infants aged 6 to 14 weeks at the time of the first dose.

Rationale Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) in young children in both developed and developing countries. The heavy global health burden prompted the development of vaccines against rotavirus illness. GlaxoSmithKline (GSK) Biologicals therefore aims to develop a safe and efficacious rotavirus vaccine that can be used with routine childhood vaccines to meet this health need.

GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. This vaccine has been tested extensively in Phase I, II and III trials and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.

This study will evaluate the efficacy, safety and immunogenicity of GSK Biologicals' HRV study vaccine at the selected optimum dose in healthy infants and will provide specific data in the European setting. The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis during the period starting 2 weeks after the second dose of study vaccination and ending at Visit 5 (mid-June to end-July 2005). Efficacy evaluation will continue during a second efficacy follow-up period ending at Visit 7 (mid-June to end-July 2006). The total study length will thus be approximately 22 months and will not exceed a total of maximum of 24 months.

This study will also assess the immune response to concomitantly administered childhood vaccinations. The co-administration of routine childhood vaccines with the HRV vaccine has been studied in other trials and no interference on immunogenicity was found. However, co-administration of some specific combination childhood vaccines in use in Europe has not been tested yet. This study will therefore evaluate concomitant administration of specific childhood vaccines currently recommended in Europe. Subjects in each participating country will receive combination childhood vaccines that comply with the current local national Plan of Immunization schedule concomitantly with each HRV vaccine or placebo dose.

The study will further evaluate factors that are useful in understanding

the epidemiology of rotavirus infections in a European context.

Objectives **Primary**

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Definitions

GE: Diarrhea with or without vomiting.

RV GE for efficacy analysis: An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.

Severe RV GE: An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system [Ruuska, 1990]). Additional alternative scoring systems may be evaluated (exploratory analyses, see Sections 8.12 and 10.6.2).

Efficacy follow-up period: All subjects will be followed over two efficacy follow-up periods. Study enrolment will start September 2004. The first efficacy follow-up period will begin 2 weeks after Dose 2 of study vaccination and end at Visit 5 (mid-June to end-July 2005). The second efficacy follow-up period will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006) covering approximately 12 months.

Also, refer to Glossary of Terms for definition of terms used.

Secondary

Efficacy

First efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations

against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- To assess vaccine efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season.

Second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice,

visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Combined efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in the immunogenicity and reactogenicity subset, N=1800)

- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccines (depending on the vaccination schedule in respective participating countries, Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® or Meningitec® vaccines will be co-administered; in case of problems with availability of Meningetec® a similar alternative that is approved in Spain can be considered).

Safety and reactogenicity

- In the immunogenicity and reactogenicity subset (N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (31 days after each dose) and serious adverse events during the entire course of the study.

Study design

- Experimental design: Double-blind, randomized, placebo-controlled, multi-country and multi-center study with two parallel groups.
- Control: Placebo (The placebo consist of all components of the study vaccine i.e. excipients and buffer, but no rotavirus particles).
- Blinding: Double-blind. See section 6.5 for details of blinding procedure.
- Treatment allocation: Randomized (2:1 ratio). See section 6.4 for a detailed description of the randomization method.
- Treatment Groups:

  Group HRV vaccine (N=2660): subjects will receive two doses of HRV vaccine co-administered with specific childhood vaccines

  Group Placebo (N=1330): subjects will receive two doses of placebo co-administered with specific childhood vaccines

- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months
  Finland: 3, 5, ***11***-12 months **(Amendment 1: 07 June 2005)**
  France and Germany: 2, 3, 4 months.
  Italy: 3, 5, 11 months
  Spain: 2, 4, 6 months

- Vaccination schedule: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.
- Concomitant vaccinations:

➢ In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing

diphtheria and tetanus toxoids and acellular pertussis (DTPa), *Haemophilus influenzae* type b (Hib), Hepatitis B vaccine (HBV), and inactivated poliovirus vaccine (IPV)] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

- In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

  - Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
  - Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

  Thereafter, routine vaccinations will be given as per the recommended respective national Plan of Immunisation schedule of each country.

- Study visits: All subjects will have five study visits (Visits 1, 2, 3, 5 and 7). Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** have ***if necessary*** one additional visit (Visit 6). **(Amendment 1: 07 June 2005)**

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=1800), Dose 1 (HRV vaccine or placebo) and Dose 1 specific childhood vaccines.

  Visit 2 (Month 1 or 2) – Dose 2 (HRV vaccine or placebo), Dose 2 specific childhood vaccines, follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Visit 3 (Month 3 or 4) – Post-vaccination blood sample from a subset of subjects (N=1800), follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and

follow-up for safety.

Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines. The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain, Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). Subjects in the Czech Republic, France and Germany will not require a separate visit since the blood sampling at post Dose 3 of the childhood vaccines coincides with Visit 3. **(Amendment 1: 07 June 2005)**

Visit 4 ("immunogenicity and reactogenicity subset" in Spain only) one month after the third dose of the primary vaccination course at 7 months of age – Post-vaccination blood sample from all subjects in Spain (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 5 (mid-June to end-July 2005) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Visit 6 ("immunogenicity and reactogenicity subset" in Italy and Finland only) one month after the third dose of the primary vaccination course

In Italy: Visit 6 at 12 months of age – Post-vaccination blood sample from all subjects in Italy (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

In Finland: Visit 6 at 13 months of age – Post-vaccination blood sample from a subset of subjects (N=300), follow-up for GE episodes with return of any GE cards and follow-up for

safety (SAEs).

Visit 7 (mid-June to end-July 2006) – Follow-up for GE episodes with return of any GE cards, follow-up for safety (SAEs) and study conclusion.

- Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject’s parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

  For each GE episode occurring during the study period, a GE diary card should be completed daily until end of the GE symptoms. During each GE episode, a stool sample(s) should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms.

- Specific solicited symptoms occurring during the 8-day follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo will be recorded by parents/guardians of a subset of subjects (N=1800) using diary cards. Unsolicited symptoms occurring within 31 days (Day 0-Day 30) after each study vaccine dose and SAEs during the entire study period will be recorded in all subjects. Parents/guardians will be asked to contact the investigator or his/her delegate in case of SAEs or IS during the study. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as contact through telephone call, SMS using cellular phone, an Independent Calling Centre or other convenient means).

- An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case is reviewed by this committee.

- Duration of the study: Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per

subject, will not exceed a total of maximum of 24 months.

- Data collection: Remote Data Entry (RDE).
- Refer to Appendix C for a summary of the recruitment plan.

Number of subjects

Total target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group).

All enrolled subjects will be followed for efficacy and safety.

Subjects will be enrolled at multiple sites in up to six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain). A target total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.

A subset of 1800 subjects (target 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Secondary endpoints

Efficacy during the first efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first

efficacy follow-up period.

- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season.

Efficacy during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Efficacy during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined

efficacy follow-up period.

- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in a subset of subjects, N=1800)

- Serum rotavirus IgA antibody concentration expressed as GMC at Visit 1 and Visit 3.
- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3.

  Seroconversion is defined as 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) seronegative for rotavirus.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccines at Visit 3 and Visit 4 or Visit 6 (if applicable):
  - Serum concentration/titer expressed as GMC/Ts for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP, anti-HBs, anti-Men C or antibodies to the 7 *Streptococcus pneumoniae* serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-polio type 1 antibody titers ≥ 8
    - anti-polio type 2 antibody titers ≥ 8
    - anti-polio type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml

- anti-HBs antibody concentrations ≥ 10.0 mIU/ml
- *Neisseria meningitidis* C serum bactericidal activity titer ≥ 1/8
- ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥0.3 mcg/ml*** **(Amendment 1: 07 June 2005)**
- antibody concentrations to *Streptococcus pneumoniae* serotypes 4, 9V,14, 18C, 23 F, 6B, 19F ≥ 0.05 mcg/ml

- Seropositivity status:
  - anti-PT antibody concentrations ≥ 5 EL.U/ml
  - anti-FHA antibody concentrations ≥ 5 EL.U/ml
  - anti-PRN antibody concentrations ≥ 5 EL.U/ml

Safety and reactogenicity

- In a subset of subjects (N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccines.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccines, according to the MedDRA classification.
- For all subjects, occurrence of serious adverse events throughout the entire study period.

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List of Abbreviations

AE	Adverse event
ATP	According-to-protocol
CCID50	median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CI	Confidence Interval
CRA	Clinical Research Associate
CSC	Central Study Coordinator
D	Diphtheria toxoid
DCSI	Development Core Safety Information
DMEM	Dulbecco's Modified Eagle Medium
DTPa	Diphtheria and tetanus toxoids and acellular pertussis
eCRF	Electronic Case Report Form
ED50	Estimated dose 50%
EISR	Expedited Investigator Safety Report
ELISA	Enzyme Linked ImmunoSorbent Assay
EL.U	Elisa units
EPI	Expanded Program on Immunization
FHA	Filamentous haemagglutinin
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC/T	Geometric Mean Concentration/Titers
GSK	GlaxoSmithKline
HBV	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus

HRV	Human Rotavirus
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPV	Inactivated poliovirus vaccine
IRB	Institutional Review Board
IS	Intussusception
IU	International Units
MedDRA	Medical Dictionary for Regulatory Activities
PID	Patient Identification Number
PMS	Post marketing surveillance
PRN	Pertactin
PRP	Polyribosyl ribitol phosphate
PT	Pertussis toxoid
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SMS	Short Message Service
SOP	Standard Operating Procedures
T	Tetanus toxoid
U	Units

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. Partially blind is to be used for study designs with different blinding levels between different groups, e.g. double blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring proper conduct of a clinical study.
Completed:	Subject who complete the final study visit foreseen in the protocol.
Diarrhea:	Passage of three or more looser than normal stools within a day.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.4 and 10.4 for details on criteria for evaluability).
First efficacy follow-up period:	Period starting from two weeks after Dose 2 of study vaccine or placebo and ending at Visit 5 (mid-June to end-July 2005).
Gastroenteritis:	Diarrhea with or without vomiting
IDMC:	Independent Data Monitoring Committee. The IDMC is responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in

	order to reduce bias of selection
Rotavirus gastroenteritis for efficacy analysis:	An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.
Rotavirus season:	The rotavirus epidemic season is expected from beginning of December to end of May in Europe.
Second efficacy follow-up period:	Period starting on the day after Visit 5 and ending at Visit 7 (mid-June to end-July 2006).
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 units (U)/milliliter (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) seronegative for rotavirus.
Seronegative:	A subject with antibody concentration below the assay cut-off value.
Seropositive:	A subject with antibody concentration 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 (Vesikari scoring system).
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	Adverse events (AEs) to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or

	placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1. INTRODUCTION

1.1. Background

Rotavirus (RV) is the most common cause of severe diarrhea and dehydration among young children in both developed and developing countries. Reviews of epidemiological data estimate that, world-wide, RV causes approximately 138 -140 million cases of diarrhea annually accounting for 20% of outpatient or clinic visits for diarrhea, 26% of hospitalizations for diarrhea and a total of 440 000-452 000 deaths in children under 5 years of age annually [Parashar, 2003]. The majority of these deaths occur in Africa, Indian subcontinent and Latin America. Epidemiologic studies have shown that the estimated RV disease burden in different European countries is high [Vesikari, 1999; Koopmans , 1999; Mrukowicz, 1999; Johansen, 1999] and most of this burden is due to RV-associated hospitalization of young children. In Europe, the estimated RV associated hospitalization rates among children under 5 years of age vary from 1 in 33 cases of RV infection in Finland, 1 in 54 in Sweden, 1 in 65 in Poland, 1 in 74 in the Netherlands and 1 in 80 in Spain [Gil, 2004].

The significant global health burden due to RV disease in both developed and developing countries prompted the development of RV vaccines. Prevention by vaccination is considered to be critical for effective control of RV infection since only non-specific symptomatic therapies are available. A variety of approaches to the development of RV vaccines have been undertaken, with live oral attenuated vaccines receiving the most attention. One vaccine, Rotashield®, a tetravalent rhesus human reassortant RV vaccine (RRV-TV), was licensed by Wyeth-Lederle in the United States in 1998 and was granted a marketing authorization for Europe in 1999 but was withdrawn from the market in 1999 due to an increased risk of intussusception (IS) (telescoping of the intestine) shortly after its administration. GlaxoSmithKline (GSK) Biologicals therefore aims to develop a safe and efficacious human rotavirus vaccine to meet this health need. GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old infant with a mild RV diarrhea in Cincinnati, United States. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilized HRV vaccine containing RIX4414 cloned from 89-12 at passage 43 for oral administration after reconstitution with buffer. The parent 89-12 vaccine was well-tolerated, immunogenic and effective in preventing RV GE among vaccinated infants during a trial in the United States [Bernstein, 1998; Bernstein , 1999; Bernstein, 2002].

GSK's RIX4414 candidate HRV differs from Rotashield®, because it is based on a human strain, whereas Rotashield® was based on a rhesus strain. There are major differences in terms of biological properties and clinical symptoms between animal (rhesus) and human RV strains, while only minor differences are expected between the attenuated RIX4414 HRV strain and the wild-type HRV. Wild-type HRV has not been associated with IS in infants. The most powerful evidence refuting a link between wild type HRV infection and IS is the absence of an increase in IS rates during the sharply defined winter RV epidemics that occur in temperate climates [Rennels , 1998]. The

RIX4414 human strain in GSK Biologicals' candidate HRV vaccine is attenuated and the attenuation might further decrease any possible, albeit unlikely, link to IS. Administration of GSK's HRV vaccine candidate does not induce a viral exposure that would otherwise not occur, in contrast with the administration of the rhesus rotavirus vaccine which represents a virus that would not normally infect children. The potential risk for the induction of IS by RIX4414 is being currently studied in large Phase III trials and the results will be available before the first enrolment in this study.

Clinical results of the GSK Biologicals HRV vaccine

GSK Biologicals' HRV vaccine has been tested in Phase I-III clinical studies and shown to be immunogenic, efficacious, safe and well-tolerated with only mild side effects in adults, previously infected children (1-3 years old) and infants. Below is a short overview of the immunogenicity, efficacy, reactogenicity and safety results of the currently completed studies.

Immunogenicity and reactogenicity

In two placebo-controlled, double-blind clinical studies conducted in Finland, infants received two doses of the vaccine at approximately 2 and 4 months of age. GSK Biologicals' HRV vaccine was immunogenic in terms of anti-rotavirus IgA antibody seroconversion rate and geometric mean antibody concentrations (GMC). RV shedding was observed in 37.5-60% of the subjects at 7-9 days after the first dose.

Results from the first pilot efficacy study in Finland (Study 004) showed that two doses of the HRV vaccine were effective in preventing RV GE. The vaccine showed 71.6% (95% confidence interval (CI): 41.6-86.8) efficacy in preventing any RV GE and 84.9% (95% CI: 41.5-97.3) efficacy in preventing severe RV GE (an episode with a score ≥ 11 on the 20-point Vesikari scale [Ruuska, 1990]) during the entire follow-up period over two RV epidemic seasons after vaccination. Of note, G1 serotype was the most prevalent circulating serotype during both RV epidemic seasons.

Results from a phase IIb, double-blind, randomized, placebo-controlled study (Study 006) in Latin America (Brazil, Mexico and Venezuela) confirmed the efficacy of the HRV vaccine in preventing RV GE in infants in a setting with different circulating serotypes. This study assessed the reactogenicity, safety, immunogenicity and efficacy of two doses of the HRV vaccine at three virus concentrations ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu) in healthy infants when given at approximately 2 and 4 months of age concomitantly with routine vaccinations (i.e. diphtheria and tetanus toxoids, whole-cell pertussis and hepatitis B [DTPw-HB] and Hib). For the first year efficacy follow-up, the protective efficacy of the HRV vaccine (pooled HRV vaccine groups), in a setting where G1 and non-G1 serotypes circulate, was 61.4% (95% CI: 42.3-74.1) against any RV diarrhea, 74.1% (95% CI: 55.8-85.0) against severe RV diarrhea (an episode with a score $\geq$11 on the 20-point Vesikari scale [Ruuska, 1990] (refer to Table 12) and 79.0% (95% CI: 48.0-92.0) against hospitalized RV diarrhea. The best protective profile against severe RV disease was observed with the viral concentration of $10^{5.2}$ ffu or higher. This allowed for the dose selection for the phase III trial ($10^{5.8}$ ffu): the protective efficacy of the $10^{5.8}$ ffu HRV vaccine group (N=463) was 70.0% (95% CI: 45.7-84.4) against any RV diarrhea, 85.6% (95% CI: 63.0-95.6) against severe RV diarrhea and 79.0% (95% CI: 24.9-96.1) against

hospitalized RV diarrhea. The vaccine efficacy against severe RV GE for the pooled HRV vaccine groups was 78.1% (95% CI: -91.1-98.2) for the second year efficacy follow-up and 74.7% (95% CI: 37.7-90.1%) for the combined efficacy follow-up periods.

In the above mentioned studies the adverse events observed in infants vaccinated with the HRV vaccine were similar to those observed in the placebo group. Additional clinical trials have been also conducted in Singapore and South Africa. The HRV vaccine was co-administered with routine recommended vaccines and found to be well-tolerated and immunogenic.

Safety

As of 31 March 2004, over 74,450 infants have been enrolled in clinical trials with GSK Biologicals' HRV vaccine and a total of 2720 serious adverse events (SAEs) have been reported. Up to 31 March 2004, 28 SAEs have been reported as possibly related to HRV vaccination.

In view of the history of Rotashield® as discussed above, IS is a particular point of interest in the safety evaluation. A large phase III multi-country trial rota-023 is ongoing in Latin America and Finland. The main focus of this study is safety and occurrence of IS. Over 63,000 children are enrolled in this study and data remain blinded at this time. An Independent Data Monitoring Committee (IDMC) has been appointed to monitor the safety aspects in all trials and that includes a review of all SAE unblinded by treatment group, all case fatalities, and all IS cases during the HRV vaccine clinical development trials, including study rota 023.

As of 18 May 2004, IS has been identified in 39 children in the entire HRV development program**.** Four of these 39 cases have been unblinded. Two of these unblinded cases (one in the placebo group and one in the HRV vaccine group) occurred remotely from vaccination: one case at 6 months and the other one at 11 months after vaccination. The two other unblinded cases (both in the HRV vaccine group) occurred at respectively 6 and 15 days post-vaccination. Of the 35 cases that are still blinded, 33 cases were reported by HRV vaccine or placebo recipients in the ongoing rota-023 study. Of these 33 cases, 17 cases occurred remotely from vaccination (at least 41 days post vaccination), 2 cases occurred between Day 31 and Day 40 post vaccination and 14 cases were in the 0-30 Day risk window. For these 33 blinded cases it is not known to the study sponsor if the children received HRV vaccine or placebo. All IS cases were diagnosed promptly and treated immediately. Most children recovered completely and are in good health. The IDMC is reviewing all data on an ongoing basis and has expressed no safety concerns up to their last review through a statement issued in May 2004. The IDMC will continue to monitor all new data also during the course of this study rota 036.

Please refer to the latest version of the investigator brochure (Edition 5) for a detailed review of information on the HRV vaccine

1.2. Rationale for the study

This study will evaluate the efficacy, safety and immunogenicity of GSK Biologicals' HRV study vaccine at the selected optimum dose in healthy infants and will provide specific data in the European setting. The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis during the period starting 2 weeks after the second dose of study vaccination and ending at Visit 5 (mid-June to end-July 2005). Efficacy evaluation will continue during the second efficacy follow-up period that will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006).

This study will also assess the immune response to concomitantly administered childhood vaccinations. The co-administration of routine childhood vaccines with the HRV vaccine has been studied in other trials and no interference on immunogenicity was found. However, co-administration of some specific combination childhood vaccines in use in Europe has not been tested yet. This study will therefore evaluate concomitant administration of some specific childhood vaccines currently recommended in Europe. Subjects in each participating country will receive combination childhood vaccines that comply with the current local national Plan of Immunization schedule concomitantly with each HRV vaccine or placebo dose.

This study will further evaluate factors that are useful in understanding the epidemiology of RV infections in a European context, e.g. age of child at time of first RV infection, influence of breastfeeding, number of siblings and attendance to day care as risk factor. To that effect additional data such as demography and feeding practices will be collected for exploratory analyses.

2. OBJECTIVES

2.1. Primary objective

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Definitions

GE: Diarrhea with or without vomiting.

RV GE for efficacy analysis: An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.

Severe RV GE: An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system [Ruuska, 1990]). Additional alternative scoring systems may be evaluated (exploratory analyses, see Sections 8.12 and 10.6.2).

Efficacy follow-up period: All subjects will be followed over two efficacy follow-up periods. Study enrolment will start September 2004. The first efficacy follow-up period will begin 2 weeks after Dose 2 of study vaccination and end at Visit 5 (mid-June to end-July 2005). The second efficacy follow-up period will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006) covering approximately 12 months.

Also, refer to Glossary of Terms for definition of terms used.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

Efficacy

First efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- To assess vaccine efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season.

Second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Combined efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or

hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in the immunogenicity and reactogenicity subset, N=1800)

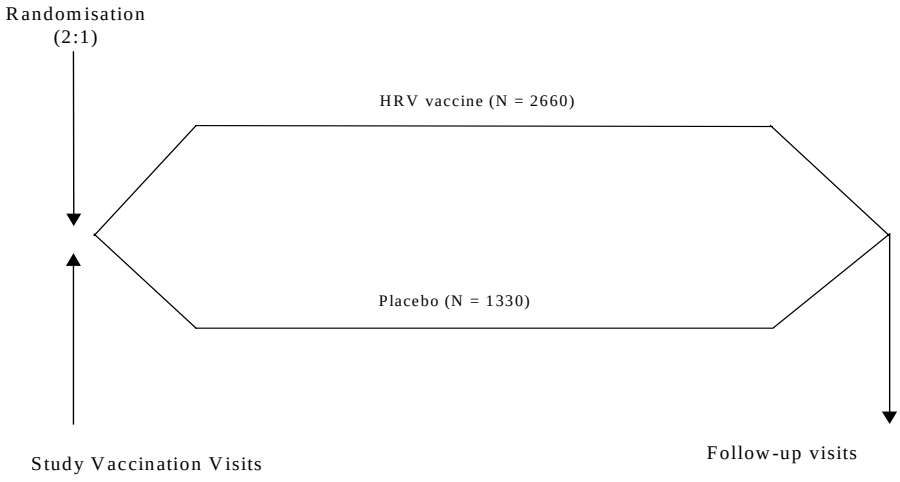
- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccines (depending on the vaccination schedule in respective participating countries, Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® or Meningitec® vaccines will be co-administered; in case of problems with availability of Meningetec® a similar alternative that is approved in Spain can be considered).

Safety and reactogenicity

- In the immunogenicity and reactogenicity subset (N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (31 days after each dose) and serious adverse events during the entire course of the study.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW



*At 7 months of age only for subjects from Spain ***(optional)***.
#At 12 months of age only for subjects from Italy ***(optional)***. At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" ***(optional)***. **(Amendment 1: 07 June 2005)**

- Experimental design: Double-blind, randomized, placebo-controlled, multi-country and multi-center study with two parallel groups.
- Control: Placebo (The placebo consist of all components of the study vaccine i.e. excipients and buffer, but no rotavirus particles).
- Blinding: Double-blind. See section 6.5 for details of blinding procedure.
- Treatment allocation: Randomized (2:1 ratio). See section 6.4 for a detailed description of the randomization method.
- Treatment Groups:

  Group HRV vaccine (N=2660): subjects will receive two doses of HRV vaccine co-administered with specific childhood vaccines

  Group Placebo (N=1330): subjects will receive two doses of placebo co-administered with specific childhood vaccines

- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months
  Finland: 3, 5, ***11***-12 months **(Amendment 1: 07 June 2005)**
  France and Germany: 2, 3, 4 months.
  Italy: 3, 5, 11 months
  Spain: 2, 4, 6 months

- Vaccination schedule: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.
- Concomitant vaccinations:

➢ In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing diphtheria and tetanus toxoids and acellular pertussis (DTPa), *Haemophilus influenzae* type b (Hib), Hepatitis B vaccine (HBV), and inactivated poliovirus vaccine (IPV)] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

- In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

  - Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
  - Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

  Thereafter, routine vaccinations will be given as per the recommended respective national Plan of Immunisation schedule of each country.

- Study visits: All subjects will have five study visits (Visits 1, 2, 3, 5 and 7). Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** have ***if necessary*** one additional visit (Visit 6). **(Amendment 1: 07 June 2005)**

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=1800), Dose 1 (HRV vaccine or placebo) and Dose 1 specific childhood vaccines.

  Visit 2 (Month 1 or 2) – Dose 2 (HRV vaccine or placebo), Dose 2 specific childhood vaccines, follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Visit 3 (Month 3 or 4) – Post-vaccination blood sample from a subset of subjects (N=1800), follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

  Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines. The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain, Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). Subjects in the Czech Republic, France and Germany will not require a separate visit since the blood sampling at post Dose 3 of the childhood vaccines coincides with Visit 3.

  Visit 4 ("immunogenicity and reactogenicity subset" in Spain only) one month after the third dose of the primary vaccination course at 7 months of age – Post-vaccination blood sample from all subjects in Spain (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 5 (mid-June to end-July 2005) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Visit 6 ("immunogenicity and reactogenicity subset" in Italy and Finland only) one month after the third dose of the primary vaccination course

In Italy: Visit 6 at 12 months of age – Post-vaccination blood sample from all subjects in Italy (N= 300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

In Finland: Visit 6 at 13 months of age – Post-vaccination blood sample from a subset of subjects (N= 300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 7 (mid-June to end-July 2006) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs) and study conclusion.

- Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject’s parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

  For each GE episode occurring during the study period, a GE diary card should be completed daily until end of the GE symptoms. During each GE episode, a stool sample(s) should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms.

- Specific solicited symptoms occurring during the 8-day follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo will be recorded by parents/guardians of a subset of subjects (N=1800) using diary cards. Unsolicited symptoms occurring within 31 days (Day 0-Day 30) after each study vaccine dose and SAEs during the entire study period will be recorded in all subjects. Parents/guardians will be asked to contact the investigator or his/her delegate in case of SAEs or IS during the study. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as

contact through telephone call, SMS using cellular phone, an Independent Calling Centre or other convenient means).

- An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case is reviewed by this committee.
- Duration of the study: Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per subject, will not exceed a total of maximum of 24 months.
- Data collection: Remote Data Entry (RDE).
- Refer to Appendix C for a summary of the recruitment plan.

4. STUDY COHORT

4.1. Number of subjects / centres

Total target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group). Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

All enrolled subjects will be followed for efficacy and safety.

Subjects will be enrolled at multiple sites in up to six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain). A target total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.

A subset of 1800 subjects (target 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

Enrolment will be terminated when 3990 subjects have been enrolled.

Refer to Appendix C for a summary of the recruitment plan.

4.2. Inclusion criteria

All subjects must satisfy the following criteria at study entry:

- Subjects who the investigator believes that their parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits, collection of stool samples) should be enrolled in the study.
- A male or female between, and including, 6 and 14 weeks (42 – 104 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Birth weight > 2000g.

4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If any apply, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)
- History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B disease (in all subjects). Only for subjects in Spain: history of meningococcal group C disease. Only for subjects in France and Germany: history of disease caused by *Streptococcus pneumoniae*.
- History of use of experimental rotavirus vaccine.
- Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (in all subjects). Only for subjects in Spain: previous vaccination against meningococcal group C. Only for subjects in France and Germany: previous vaccination against *Streptococcus pneumoniae*.
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract, IS or other medical condition determined to be serious by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

- Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).)
- Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).
- A family history of congenital or hereditary immunodeficiency.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- History of any neurologic disorders or seizures.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests

4.4. Elimination criteria during the study

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants 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 study vaccine(s) and ending 14 days after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

4.5. Contraindications to subsequent vaccination

GSK Biologicals' HRV vaccine or placebo:

The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 0):

- Hypersensitivity reaction due to the vaccine.
- IS.

The following AEs constitute contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs 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 5.4), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).

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

Co-administered vaccines:

For detailed information on Infanrix Hexa®, Infanrix Polio Hib®, *Neisseria meningitidis* C vaccine (e.g. Meningitec®) and *Streptococcus pneumoniae* vaccine (e.g. Prevenar®) to be co-administered with HRV vaccine or placebo, please consult the summary of product characteristics of the respective product in each country.

DTP vaccines (including Infanrix Hexa® and Infanrix Polio Hib®)

The following AEs constitute absolute contraindications to further administration of DTP vaccine; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine 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 AE:

Absolute contra-indications:

- Hypersensitivity reaction due to the vaccine.
- Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.

The following AEs constitute contraindications to administration of the study vaccine at that point in time; if any one of these AEs 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 AE.

- Acute disease at the time of vaccination. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).

- Axillary temperature ≥37.5°C (99.5°F) / Rectal temperature ≥38°C (100.4°F) / Oral temperature ≥37.5°C (99.5°F).

Precautions:

- Fever of ≥40.5°C (rectal temperature) or ≥40.0°C (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 occurring within 48 hours of vaccination and lasting ≥ 3 hours.
- Seizures with or without fever occurring within 3 days of vaccination.

Meningitec®

Absolute contraindications include:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- Acute severe febrile illness.

Prevenar®

Absolute contraindications include:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- Acute severe febrile illness.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 version of 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. The ICH Harmonized Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. 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 provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator and/or sponsor.

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 the IRB/IEC by the investigator and/or sponsor. Written unconditional approval of the IRB/IEC must be in the possession of the investigator and GSK Biologicals before commencement of the study. 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. Relevant GSK Biologicals' data will be supplied by the investigator and/or sponsor to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of IRB/IEC unconditional approval of the protocol and the written informed consent statement will be transmitted by the investigator to the Site Monitor using the standard notification form, prior to shipment of vaccine supplies and the electronic case report forms (eCRFs)/RDE system to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval of an appropriate amendment. Administrative changes are submitted to the IRB/IEC for information only. However, written verification that the administrative change was submitted should be obtained. Approvals/ verifications must be transmitted in writing to the Site Monitor by the investigator.

The IRB/IEC must be informed by the investigator and/or sponsor of:

- all subsequent protocol amendments, 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 administrative changes (for information, except for US studies),
- 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.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator and/or sponsor must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical

principles that have their origin in the October 1996 version of the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to the subjects' parents/guardians.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects' parents/guardians face to face. The Informed Consent Form may be read to the subjects' parents/guardians, but, in any event, the investigator or designate shall give the subjects' parents/guardians ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects' 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 parents/guardians and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the parents'/guardians' incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The parents/guardians should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects' parents/guardians, and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects' parents/guardians.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects' parents/guardians should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's parents'/guardians' responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects' parents/guardians should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects' parents/guardians for participating in the trial.

l. The anticipated expenses, if any, to subjects' parents/guardians for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects' parents/guardians may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the 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 subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject's parents/guardians is authorizing such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects' parents/guardians will be informed in a timely manner if information becomes available that may be relevant to the subjects' parents/guardians willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent

form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. General study aspects

- There will be no restrictions on feeding the infants before or after study vaccine administration.
- All vaccines administered in the period beginning at birth and ending at the blood sampling visit after completion of the routine three-dose primary vaccination course should be documented in the eCRF.
- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months
  Finland: 3, 5, ***11***-12 months **(Amendment 1: 07 June 2005)**
  France and Germany: 2, 3, 4 months.
  Italy: 3, 5, 11 months
  Spain: 2, 4, 6 months

- In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing DTPa, HBV, Hib and IPV] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

- In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

  - Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
  - Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

  Thereafter, routine vaccinations will be given as per the recommended local national Plan of Immunisation schedule.

- All subjects in all countries will have five study visits (Visits 1, 2, 3, 5 and 7). In addition, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" (target N=300 per country) ***may*** have ***if necessary*** an additional study visit because the blood sampling timepoint one month post Dose 3

of the childhood vaccines in these countries does not ***always*** coincide with study visits planned for all subjects. Blood samples will be taken at the additional visit to evaluate immunogenicity of routine vaccines The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain, Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). **(Amendment 1: 07 June 2005)**

- The study will further evaluate factors that are useful in understanding the epidemiology of RV infections in a European context, e.g. age of child at time of first RV infection, influence of breastfeeding, number of siblings and attendance to day care as risk factor. To that effect additional data will be collected, at the time of the scheduled visits or using the GE diary cards.

5.2.1. Independent Data Monitoring Committee (IDMC)

An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case and each case fatality is reviewed unblinded by treatment group by this committee.

5.2.2. Surveillance of SAEs and IS

Parents/guardians of all subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as contact through the Independent Calling Centre or another convenient means).

The investigators will be asked to inform the parents/guardians of the signs and symptoms of IS. Symptoms consistent with IS are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. Parents/guardians/caretakers of study subjects will be instructed to seek medical advice at the nearest hospital in case of symptoms indicative of IS, and to inform the investigator. The investigator and his staff will take appropriate actions to treat the condition. Refer to Appendix H for information on follow-up of IS cases and refer to Appendix D for information on handling of biological samples collected during IS cases.

5.2.3. Follow-up of GE episodes and collection of stool samples

Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to

end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

For each suspected GE episode occurring during the study period, a GE diary card should be completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE episode will be recorded on the same card. The completed diary cards should be returned to the investigator at the following study visit. The investigator will verify the returned completed GE diary card and (s)he or study personnel will transcribe the information into the appropriate sections of the eCRF, in English.

For each suspected GE episode occurring during the study period, a stool sample should be obtained from the subject. The stool sample should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms. The stool sample should be stored at refrigerator temperature (approximately 2-8°C) until it is transferred rapidly to the investigator's laboratory (within 0-3 days). The stool sample should be stored frozen at approximately - 20°C or colder until shipped to GSK Biologicals (Please refer to Appendix D and Appendix E).

5.3. Subject identification

Subject numbers will be assigned sequentially to subjects contacted by study investigators, according to the range of subject numbers allocated to each study centre. Refer to Section 6.4 for a detailed description of treatment allocation and randomization.

5.4. Outline of study procedures

Table 1 List of study procedures at visits planned for all subjects in all countries

(Amendment 1: 07 June 2005)

Age **Visit §** **Timing** **Sampling timepoint**	**6-14 weeks** **VISIT 1** **Day 0** **Pre**	**VISIT 2** **Month 1 or 2**	**VISIT 3** **Month 3 or 4** **Post vacc 2**	**VISIT 5**	**VISIT 7**
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●‡		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in a subset: for antibody determination	● (1 ml) (N=1800)		● (3 ml) (N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations∗	●	●			
Recording all childhood vaccinations	●	●	●	● ***Finland/Italy only***	
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)	●	●			
Return of reactogenicity diary cards in a subset (N=1800)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination#	●	●	●	●	
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●
Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

§Additional visits ***can be*** planned ***if necessary*** for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset": Visit 4 will take place in Spain only and Visit 6 take place in Finland and Italy only. Visit 4 and Visit 6 are not applicable for France, Germany and the Czech Republic. Refer to Table 2 for more details. **(Amendment 1: 07 June 2005)**

Note: The double-line border following Month 3 indicates the interim analysis which will be performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.

● is used to indicate a study procedure that requires documentation in the individual eCRF.
‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**
∗ The third dose of the routine childhood vaccine(s) must be given according to the respective national Immunisation plans of each country. A study visit is not planned specifically for administration of third dose of the routine childhood vaccine(s).
#According to guidelines specified in Section 6.9
¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

(Amendment 1: 07 June 2005)

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2∗	VISIT 6 ITALY only Month 9 Post-vacc 2∗	 FINLAND only Month 10 Post-vacc 2∗
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●‡	●‡	●‡
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in a subset: for antibody determination (3 ml)	● (target N=300 from Spain)	● (target N=300 from Italy)	● (target N=300 from Finland)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)			
Return of reactogenicity diary cards in a subset (N=1800)			
Transcription of the reactogenicity diary card in a subset (N=1800)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination#	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of routine childhood vaccinations.

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

#According to guidelines specified in Section 6.9

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject's evaluability in the according to protocol analyses (see Sections 4.4 and 10.4 for details of criteria for evaluability and cohorts to be analyzed).

The local national Plan of Immunization schedules vary from country to country. The local immunization schedule should be followed to administer study vaccine concomitantly with specific childhood vaccinations at Visit 1 and Visit 2. In order to assess the safety of the study vaccine, the interval between two study vaccine doses should not be less than 30 days. Table 3 presents the interval between study visits to be followed in each specified country. Table 4 presents the age at each visit per country.

Table 3 Intervals between study visits

(Amendment 1: 07 June 2005)

Interval	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Routine schedule	**3, 4, 5 months**	**3, 5, *11*-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccines
End of the 1st efficacy follow-up period	mid-June to end-July 2005				
one month after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable
End of the 2nd efficacy follow-up period	mid-June to end-July 2006				

Table 4 Age of the subjects at each study visits

Age at Visit	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Visit 1	3 months	3 months	2 months	3 months	2 months
Visit 2	4 months	5 months	3 months	5 months	4 months
Visit 3	6 months	6 months	5 months	6 months	6 months
Visit 4	Not applicable				7 months
Visit 5	Will vary (Visit to be completed by mid-June to end-July 2005)				
Visit 6	Not applicable	13 months	Not applicable	12 months	Not applicable
Visit 7	Will vary (Visit to be completed by mid-June to end-July 2006)				

5.5. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

Visit 1: Dose 1 of study vaccine (6-14 weeks of age)

- Written informed consent from the parent/guardian of the subject.
- Medical history taking.
- Physical examination and recording of height and weight.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Check of inclusion/exclusion criteria.
- Check contraindications to vaccination.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF.
- Record feeding practice.
- Randomization (or subject) number attribution.
- Collection of pre-vaccination blood sample for serology from a subset of subjects (N=1800): a minimum of 1 ml of whole blood to provide a minimum of 0.6 ml of serum according to instructions in Appendix D.
- Study vaccination: Oral administration of Dose 1 of the HRV vaccine or its placebo according to the guidelines set out in Section 6.2.
- Administration of specific vaccines to be co-administered with HRV vaccine or placebo dose. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be 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.
- Diary cards will be provided to the parents/guardians of all subjects to record unsolicited AEs (except GE) and medication between Visit 1 and Visit 2. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.

- Reactogenicity diary cards will be provided to the parents/guardians of a subset of subjects (N=1800) to record specific solicited general adverse experiences occurring during the 8-day (Day 0 to Day 7) solicited follow-up period after Dose 1 of the study vaccine or placebo. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- All parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Day 8 after Dose 1 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Interval between Visit 1 and Visit 2

Day 0 to Day 7 after Dose 1:

- The parents/guardians of a subset of subjects (N=1800) should record information on specific solicited general adverse experiences in the provided reactogenicity diary card.

Between Visit 1 and Visit 2

- Starting from Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians of all subjects should record information on any unsolicited AEs (except GE) and medications in the provided diary card.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 2: Dose 2 of study vaccine (30-48 days after Visit 1 in the Czech Republic, France and Germany / 49-83 days after Visit 1 in Finland, Italy and Spain)

- Physical examination.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Check of the appropriate elimination criteria.

- Collection and verification of the completed unsolicited AE/medication diary card from all subjects.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Recording of any unsolicited AEs within 31 days (Day 0 to Day 30) after Dose 1 of the study vaccine and any SAEs/IS that may have occurred since Visit 1 in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Check contraindications to vaccination.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Collection of the completed reactogenicity diary cards from a subset of subjects (N=1800). The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Record feeding practice.
- Study vaccination: Oral administration of Dose 2 of the HRV vaccine or its placebo according to the guidelines set out in Section 6.2.
- Administration of specific vaccines to be co-administered with HRV vaccine or placebo dose. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be 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.
- Diary cards will be provided to the parents/guardians of all subjects to record unsolicited AEs (except GE) and medication between Visit 2 and Visit 3. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Reactogenicity diary cards will be provided to the parents/guardians of a subset of subjects (N=1800) to record specific solicited general adverse experiences occurring during the 8-day (Day 0 to Day 7) solicited follow-up period after Dose 2 of the study vaccine or placebo.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Day 8 after Dose 2 until the next visit. The parents/guardians will be instructed to return their completed diary cards to

the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Interval between Visit 2 and Visit 3

Day 0 to Day 7 after Dose 2:

- The parents/guardians of a subset of subjects (N=1800) should record information on specific solicited general adverse experiences in the provided reactogenicity diary card.

Between Visit 2 and Visit 3

- Until end of May 2005, each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians of all subjects should record information on any unsolicited AEs (except GE) and medications in the provided diary card.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries, including between visits if applicable. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.

Visit 3: Follow-up (30-48 days after Visit 2 in Finland and Italy / 49-83 days after Visit 2 in the Czech Republic, France, Germany and Spain)

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- Check of the appropriate elimination criteria.
- Collection and verification of the completed unsolicited AE/medication diary card from all subjects.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.

- Recording of any unsolicited symptoms within 31 days (Day 0 to Day 30) after Dose 2 of the study vaccine and any SAEs/IS that may have occurred since Visit 2 in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Collection of post-vaccination blood sample for serology from a subset of subjects (N=1800): a minimum of 3 ml of whole blood to provide a minimum of 1.2 ml of serum according to instructions in Appendix D.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Collection of the completed reactogenicity diary cards from a subset of subjects (N=1800). The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 3 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.
- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries, including at or between visits if applicable. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.

Between Visit 3 and Visit 5

- From December 2004 to end of May 2005, each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries, including between visits if applicable. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.

Visit 4 (at 7 months of age): Only for subjects in Spain.
Visit 4 is optional and may be combined with Visit 5.
(Amendment 1: 07 June 2005)

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- Check of the appropriate elimination criteria.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Collection of post-vaccination blood sample for serology from all subjects in Spain: a minimum of 3 ml of whole blood to provide a minimum of 1.2 ml of serum according to instructions in Appendix D.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 4 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Visit 5 (mid-June to end-July 2005): End of the first efficacy follow-up period

- Check of the appropriate elimination criteria.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate

sections of the electronic case report form, in English. The study monitor may help in this translation.

- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 5 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.
- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.
- Conclusion of Visit 5.

Between Visit 5 and Visit 7

- Between Visit 5 and December 2005, each subject's parent/guardian will be contacted biweekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- Between December 2005 to end of May 2006 each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE. Bi-weekly contact will take place from June 2006 until study end.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 6: Only for subjects from the "immunogenicity and reactogenicity subset" in Italy at 12 months of age and in Finland at 13 months of age.
Visit 6 is optional and may be combined with Visit 5
(Amendment 1: 07 June 2005)

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and***

appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

- Check of the appropriate elimination criteria.
- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Collection of post-vaccination blood sample for serology in a subset of subjects: a minimum of 3 ml of whole blood to provide a minimum of 1.2 ml of serum according to instructions in Appendix D.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 6 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Visit 7 (mid-June to end-July 2006): End of the second efficacy follow-up period

- Check of the appropriate elimination criteria.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Conclusion of Visit 7 and study end.

5.6. Sample handling and analysis

5.6.1. 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.

5.6.2. Laboratory assays

5.6.2.1. GE stool analysis

Stool samples collected during GE episodes will be processed at the study site and shipped frozen to GSK Biologicals, Belgium for further distribution to the core laboratories where analysis will be performed.

All GE stool samples will be analysed by ELISA for detection of RV. If a stool sample tests positive for RV, the sample will be tested by Polymerase Chain Reaction (PCR) to determine the serotype. If any G1 rotavirus is detected in the stool specimens between Visit 1 to Visit 3, vaccine virus will be differentiated from the wild type serotype by sequence analysis or an equivalent approach.

Any additional testing on stool samples will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine

5.6.2.2. Serum analysis

Refer to Section 6.4.3 for information on the subset of subjects who will provide blood samples. Blood samples collected from a subset of subjects at each sampling time point will be centrifuged and the separated serum should be stored at –20°C until shipped to the sponsor for analysis.

All serological assays will be performed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Anti-rotavirus IgA antibody concentrations will be measured in all serum samples collected at Visit 1 and Visit 3.

Other assays will be performed depending on the specific vaccines co-administered with each HRV vaccine or placebo dose. Antibodies to all antigens contained in the co-administered vaccines will be measured at each sampling time point [i.e. Visit 3 (all countries), Visit 4 (Spain) and Visit 6 (Italy and Finland)]. In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity ***and ELISA test***, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP. **(Amendment 1: 07 June 2005)**

Table 5 summarizes the laboratory assays to be performed on the serum samples.

Table 5 Laboratory Assays

(Amendment 1: 07 June 2005)

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
rotavirus	IgA ELISA	in-house	U/ml	20
anti-D	ELISA	in-house	IU/ml	0.1
anti-T	ELISA	in-house	IU/ml	0.1
anti-PT	ELISA	in-house	EL.U/ml	5
anti-FHA	ELISA	in-house	EL.U/ml	5
anti-PRN	ELISA	in-house	EL.U/ml	5
anti-HBs	ELISA	in-house	mcg/ml	10
anti-poliovirus type 1	micro-neutralization test	in-house	ED50	8
anti-poliovirus type 2	micro-neutralization test	in-house	ED50	8
anti-poliovirus type 3	micro-neutralization test	in-house	ED50	8
anti-PRP	ELISA	in-house	mcg/ml	0.15
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	***In-house***	***mcg/ml***	***0.3***
Antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide*	ELISA	in-house	mcg/ml	0.05

U = units
IU = International units
EL.U = Elisa units
ED 50 = Estimated dose 50%
#For samples from Spain only
*For samples from France and Germany only

Any additional testing on serum samples will be performed if deemed necessary by GSK Biologicals if any findings concerning toxicity or immunogenicity in the present study or in other studies necessitate further investigations.

Refer to Appendix F for details on laboratory assays.

5.6.3. IS samples

Refer to Appendix H for information on analysis of biological samples collected for IS.

The GSK Biologicals' designated laboratories will test:

- Frozen stool samples or rectal swab and throat swab specimens by RT-PCR to determine the presence of RV, enteroviruses and adenoviruses.

- Acute and convalescent blood samples will be tested to detect an acute antibody response to RV. Blood and/or stool and/or throat swab tests will be tested for the presence of a range of suspected pathogens. Also, histopathologic evaluation of tissue will be conducted.
- In case of surgical resection, a surgical specimen of any enlarged mesenteric lymph node should be obtained. If bowel or the appendix is resected, these specimens also should be included in the evaluation. As molecular assays are to be performed on these surgical specimens, the use of powderless gloves, RNAse-free pipettes, aerosol RNAse-free tips, non-autoclaved disposable plasticware/forceps, commercial PBS solution/water/Formaldehyde solutions as well as limited steps of the solution preparation are highly recommended to avoid RNAse contamination. Refer to the lab workbook for the process of resected tissue. Testing including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR will be arranged by GSK Biologicals in consultation with the Attending Pathologist.
- Fresh stool samples may be tested locally according to standard microbiologic methods for the presence of any suspected enteric pathogens, e.g. Salmonella, Shigella, Campylobacter, Yersinia, and others.

Any additional testing on biological samples collected for IS will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine.

5.6.4. Serology and stool analysis plan

Table 6 presents the plan for analyses of serum and stool samples collected during the study.

Table 6 Serology and Stool Analysis Plan

(Amendment 1: 07 June 2005)

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times during the study			RV	all	none
Serology					
Pre	0	1	HRV	Immunogenicity subset (N=1800)	none
Post-vacc 2∗	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP, 7 *S. pneumoniae* serotypes (France and Germany only)	Immunogenicity subset ***except Spain*** (N=1~~5~~800)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	***3***	***HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)***	***N=300 from Spain***	***HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.***
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity ***and ELISA test***	N=300 from Spain	***Men C*** serum bactericidal activity ***and ELISA test***, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	9	6 (Italy only)	, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP	N=300 from Italy	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP
	10	6 (Finland only)	, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP	N=300 from Finland	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP

∗Post Dose 2 of study vaccine for all countries. Depending on the local national Plan of Immunisation schedule in each country, may be post Dose 2 or post Dose 3 of routine childhood vaccines
#Corresponds to Post Dose 3 of routine childhood vaccines in the respective countries.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to the priority ranking specified in Table 6.

5.6.5. Endpoints for suboptimal response

Not applicable.

6. INVESTIGATIONAL PRODUCTS AND ADMINISTRATION

6.1. Study vaccines

The candidate vaccine, placebo and diluent to be used have been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for each product are described in separate release protocols and the required approvals have been obtained.

Table 7 presents the composition of the study vaccine.

Table 7 Study vaccine composition

Vaccine	Formulation	Presentation	Volume
GSK Biologicals' HRV vaccine	RIX4414 HRV strain $10^{6.5}$ CCID50 Dulbecco's Modified Eagle Medium (DMEM) 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilized vaccine in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' Placebo for HRV vaccine	DMEM 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilized vaccine in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' calcium carbonate buffer	Calcium carbonate 80 mg Xanthane 0.25 % in Water for Injection 1.3 ml	Liquid buffer in pre-filled syringe.	1.3 ml

One lot each of the HRV vaccine and placebo will be used.

GSK Biologicals' Infanrix Hexa®, Infanrix Polio Hib® ***and Prevenar***® vaccines will be also supplied. These commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics. **(Amendment 1: 07 June 2005)**

Refer to Appendix G for details of vaccine supplies.

6.2. Dosage and administration

HRV vaccine or placebo

To prepare the HRV vaccine or placebo for administration, the entire content of the supplied calcium carbonate 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.

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Should the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered at that visit. The subject may continue to participate to the study and will not be excluded from the planned analyses.

Childhood vaccines to be co-administered with each study vaccine dose

Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® and Meningitec® vaccines should be prepared and administered according to the manufacturer's recommendations.

The vaccination regimen is summarized in Table 8.

Table 8 Dosage and Administration

Country	Visit	Vaccination	Dose	Vaccine[a]	Route[b]	Site[c]
Study vaccination						
All	1, 2	Rotavirus or its Placebo	1	HRV or placebo	O	not applicable
Childhood vaccines to be co-administered with each study vaccine dose						
All, except France	1, 2	DTPa, HBV, IPV, Hib	1	Infanrix Hexa®	IM	T
France	1	DTPa, HBV, IPV, Hib	1	Infanrix Hexa®	IM	T
	2	DTPa, IPV, Hib	1	Infanrix Polio Hib®	IM	T
France and Germany	1, 2	*Streptococcus pneumoniae*	1	Prevenar®	IM	D/ T
Spain	1, 2	*Neisseria meningitidis* C	1	Meningitec®	IM	D/ T

a. Vaccine/Control
b. Oral (O)/ Intramuscular (IM)
c. Deltoid (D)/ Thigh (T)

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Thereafter, routine vaccinations will be given as per the recommended local national Plan of Immunisation schedule. Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

6.3. Storage

(Amendment 1: 07 June 2005)

All vaccines must be stored in a safe and locked place with no access for unauthorized personnel.

Vaccines will be stored at the defined range of temperature (i.e. +2 to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of temperature deviation (temperature outside the defined range, i.e. +2 to +8°C/ 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

proper functioning was demonstrated during the monitor's site evaluation,

if the system continues to work in case of a power failure, and

if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working when after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag®) close to the vaccines as a back up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C/ 36°F to 46°F), must be reported within 24 hours to the Sponsor (i.e. Study Monitor/ GSK Local Contact/ GSK Biologicals)

Following exposure to a temperature deviation, vaccines will not be used until written approval is given by the sponsor.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.

6.4. Treatment allocation and randomization

Target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group).

6.4.1. Randomization of supplies

A randomization list will be generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and will be used to number the vaccines. A randomization blocking scheme (2:1 ratio) will be used to ensure that balance between treatments is maintained: a single treatment number will identify uniquely the vaccine doses to be administered to the same subject.

To allow GSK Biologicals 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, an over-randomization of supplies (not exceeding 20%) will be prepared.

The vaccine doses will be distributed to each study centre while respecting the randomization block size.

6.4.2. Randomization of subjects

The treatment allocation at the investigator site will be performed using a central randomization call-in system on Internet (SBIR). The randomization algorithm will use a minimization procedure stratified by vaccination sites.

After confirmation that the subject is eligible, the person who is in charge of the vaccination will access the randomization system on Internet. Upon providing a subject number for the subject, the randomization system will use the minimization algorithm to determine the treatment number to be used for the subject. Would Internet be unavailable the subjects would be administered the treatment number with the highest number still available at the vaccination site.

6.4.3. Subsets

A subset of 1800 subjects (target of 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

For Finland, 300 subjects enrolled at specific centre(s) will be part of the "immunogenicity and reactogenicity subset". For each of the other participating countries, all of the 300 enrolled subjects will be part of the "immunogenicity and reactogenicity subset".

6.5. Method of blinding and breaking the study blind

The study will be conducted in a double-blinded manner. The parents/guardians of the subjects, the study personnel including the study monitor and the investigator will be unaware of the administered treatment. Blinding will be maintained for the whole study period (see Section 10.7 for details on how the individual blinding will be maintained despite statistical analyses before all study data are collected/processed). This will allow unbiased evaluation of the study vaccine.

No set of individual codes will be held at the local GSK Biologicals' Safety Office or GSK Biologicals' Central Safety Office. The local GSK Biologicals' Safety Office will be able to access the individual randomization code from the central randomization system on the Internet. The GSK Biologicals' Central Safety Office will access the

individual randomization code using Matex (new randomization system). The code will be broken by the Clinical Safety physician (Study Contact for Emergency Code Break in Sponsor Information page) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s).

In the event that the code is broken, the reason must be recorded in the eCRF/RDE and in the subject's medical record.

The IDMC will be informed of each SAE including any IS cases on an ongoing basis. The IDMC will have access to the individual codes and may at its discretion decode the SAEs to identify the product administered to any subject and evaluate whether enrollment in the study should be halted.

6.6. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix G for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 5% additional doses will be supplied. In case a vaccine dose is broken or unusable, the investigator should replace it with a replacement vaccine dose. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of the replacement vaccine must be recorded by the investigator on the vaccine administration page of the eCRF and on the vaccine accountability form.

The investigator will use the central randomization system (SBIR) to obtain the replacement vial number. The system will ensure, in a blinded manner, that the replacement vial is of the same formulation as the randomized vaccine.

6.7. Packaging

See Appendix G.

6.8. Vaccine accountability

See Appendix G.

6.9. Concomitant medication/treatment

At each study visit/contact, the investigator should question the subject's parents/guardian about any medication(s) taken.

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study

vaccine (HRV vaccine or placebo) are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever is later) are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment. Refer to Sections 4.3 and 4.4.

All vaccines administered in the period beginning at birth and ending at the blood sampling visit after completion of the routine three-dose primary vaccination course are to be recorded with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as ‘Prophylactic’.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for adverse events must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment. Refer to Section 8.2 for definition of SAE.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

Each subject’s parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.

Examples of an AE DO NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

N.B. AEs to be recorded as endpoints (solicited events) are described in Section 8.5.1. All other AEs will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study procedure) should be recorded in the medical history section of the subject's eCRF.

8.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which 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.

c. requires hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.2.1. Disease-related events or outcomes not qualifying as serious adverse events

Not applicable.

8.3. Lack of efficacy

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the AE or SAE definition (including clarifications).

8.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, ultrasound etc.) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1 or SAE, as defined in Section 8.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.5. Time period, frequency, and method of detecting adverse events and serious adverse events

All AEs occurring within 31 days following administration of each dose of vaccine/ placebo 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.

All AEs leading to subject withdrawal or drop out 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.

The standard time period for collecting and recording SAEs will begin at randomization or the first receipt of vaccine/ placebo and will end at the last study visit foreseen for each subject. See Section 8.8 for instructions for reporting and recording SAEs.

Additionally, in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. procedures, invasive tests, a change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

The investigator will inquire about the occurrence of AEs/SAEs at every visit/contact during the study.

All AEs either observed by the investigator or one of his clinical collaborators or reported by the subject's parent/guardian spontaneously or in response to a direct question will be evaluated by the investigator. AEs 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. Refer to Section 6.9.

As a consistent method of soliciting AEs, the subject's parent/guardian 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 AEs having occurred within the time frame defined above.

AEs already documented in the eCRF, i.e. at a previous assessment, and designated as "not recovered/not resolved" or "recovering/resolving" should be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the eCRF should be completed.

N.B. If an AE changes in frequency or intensity during the specified reporting period, a new record of the event will be entered.

When an AE leading to drop out/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE leading to drop out /SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed AE/SAE pages. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE leading to drop out /SAE and not the individual signs/symptoms.

8.5.1. Solicited adverse events

Solicited general AEs

Information on solicited symptoms will be collected for 8 days (Day 0 to Day 7) after each HRV vaccine or placebo dose by the parents/guardians of a subset of subjects (N=1800) using diary cards provided by the sponsor. Table 9 specifies the general AEs solicited during this study.

Table 9 Solicited general adverse events

Fever (Rectal/Axillary)
Fussiness/Irritability
Loss of appetite
Vomiting
Diarrhea
Cough/runny nose

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

8.6. Evaluating adverse events and serious adverse events

8.6.1. Assessment of intensity

Intensity of the following AEs will be assessed as described in Table 10.

Table 10 Intensity scales to be used by parents/guardians for solicited symptoms

Adverse Experience	Intensity grade	Parameter
Fever*		Record temperature in °C using a rectal/axillary 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
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 temperature ≥38°C (≥37.5°C) as measured by a rectal (axillary) thermometer.
¶Diarrhea is defined as passage of 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.

The maximum intensity of diarrhea, fever and vomiting occurring during the solicited 8-day follow-up period will be scored at GSK Biologicals as shown in Table 11.

Table 11 Intensity scales used at GSK Biologicals for diarrhea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	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
Fever	0	Rectal temperature < 38.0°C or axillary temperature < 37.5°C
	1	Rectal temperature ≥ 38.0 – ≤ 38.5°C or axillary temperature ≥ 37.5 – ≤ 38.0°C
	2	Rectal temperature > 38.5 – ≤ 39.5°C or axillary temperature > 38.0 – ≤ 39.0°C
	3	Rectal temperature > 39.5°C or axillary temperature > 39.0°C

The investigator will make an assessment of intensity for all other AEs, i.e. unsolicited symptoms reported within 31 days (Day 0-Day 31) after each study vaccine dose and AEs leading to drop out or SAEs reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE (unsolicited symptoms

or AE leading to drop out) and SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. (In a young child, such an AE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.2.

8.6.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE Report Form to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE Report Form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

Causality of all AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	The AE 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 AE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.6.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parents/guardians will be asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the eCRF.

8.7. Follow-up of adverse events and serious adverse events and assessment of outcome

After the initial AE (unsolicited symptom or AE leading to drop out)/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All AEs (unsolicited symptom or AE leading to drop out) and SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts.

Investigators will follow-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

- or, in the case of other non-serious AEs, until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE Report Form, with all changes signed and dated by the investigator. The updated SAE report form should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.8.1.

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e. unsolicited AE), AE leading to drop out or any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.8. Prompt reporting of serious adverse events to GSK Biologicals

8.8.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. The investigator or designate will fax the SAE reports to GSK Biologicals' Study Contact for Serious Adverse Event Reporting **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS**. Additional or follow-up information relating to the initial SAE report is also to be reported to the GSK Biologicals' Study Contact for Serious Adverse Event Reporting within 24 hours of receipt of such information.

8.8.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours as outlined in Section 8.8.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received and forwarded to GSK **WITHIN 24 HOURS** as outlined in Section 8.8.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.6.2.

Facsimile (Fax) transmission of the SAE Report Form is the preferred method to transmit this information to the Study Contact for Reporting SAEs. The Study Contacts per country (where available) are provided as a separate protocol attachment (refer Attachment 1); in the case where the Study Contact is not available, you must contact the back-up Study Contact (see below). In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours as outlined in Section 8.8.1.

In the event of a death determined by the investigator to be related to vaccination, sending of the fax must be accompanied by telephone call to the Study Contact for Reporting SAEs.

(Amendment 1: 07 June 2005)

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [redacted] ***or*** [redacted] **24/24 hour and 7/7 day availability**

8.9. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.8. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

Expedited Investigator Safety Reports (EISR) are prepared according to GSK Biologicals policy and are forwarded to investigators as necessary. An EISR is required for:

- development compounds (i.e. compounds not marketed), if the event is serious, unexpected and has a suspected relationship to study drug treatment. Expected adverse events for development compounds will be described in the Development Core Safety Information (DCSI) in the Investigator Brochure (IB).
- marketed compounds (i.e. approved in at least one market), if the event is serious, unexpected and has a suspected relationship to treatment with a GSK product AND is a significant new emerging safety issue. Expected adverse events for marketed compounds will be described in the Core Safety Information (CSI). An EISR is required if an SAE was expedited to the IND in the US or to fulfil regulatory obligations in other countries. An EISR for Post marketing surveillance (PMS)/phase IV studies would not typically be required.

The purpose of the EISR is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an EISR describing a SAE or other specific safety information from GSK Biologicals will file it with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.10. Post study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 8.5. Investigators are not obligated to actively seek AEs or SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.11. Pregnancy

Not applicable.

8.12. Assessment of GE episodes

Any GE episode (defined as diarrhea with or without vomiting) starting from Visit 1 to study end should be documented using the GE diary card. The following information will be collected on the GE diary card during each GE episode: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be also recorded. The information collected

on the GE diary card will allow the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

Medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) will also be recorded for each GE episode.

Behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

In the 20-point scoring system [Ruuska, 1990], points will be assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalization (hospitalized subjects will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 12.

Table 12 The 20-point scoring system to determine the intensity of GE episodes reported during the study

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode will be scored.

A score < 7 is prospectively defined as mild, a score 7 - 10 is prospectively defined as moderate and a score ≥ 11 is prospectively defined as severe [Joensuu , 1997].

Periodic contact will be made with the subjects' family to enquire about the occurrence of GE, medical care or advice, and hospitalization. Collection of a stool sample will be requested if not yet provided and if GE occurred since last contact.

8.13. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.9.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Subjects who are withdrawn for AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (see Section 0).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study is any subject who did not come back for the concluding visit foreseen in the protocol.

A subject qualifies as a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented on the Study Conclusion page of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject's parent or guardian or the investigator and which of the following possible reasons was responsible for withdrawal:

- serious adverse event
- non-serious adverse event

- protocol violation (specify)
- consent withdrawal, not due to an adverse event
- moved from the study area
- lost to follow-up
- other (specify).

9.2.2. Subject withdrawal from investigational product

A 'withdrawal' from the investigational product is any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational product may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational product will be documented on the Vaccine Administration page of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject's parent or guardian or the investigator and which of the following possible reasons was responsible for withdrawal:

- serious adverse event,
- non-serious adverse event,
- other (specify).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

10.2. Secondary endpoints

Efficacy during the first efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.

- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season.

Efficacy during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Efficacy during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in a subset of subjects, N=1800)

- Serum rotavirus IgA antibody concentration expressed as GMC at Visit 1 and Visit 3.
- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3. Refer to the glossary of terms for definition of seroconversion.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccines at Visit 3 and Visit 4 or Visit 6 (if applicable):
  - Serum concentration/titer expressed as GMC/Ts for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP, anti-HBs, anti-Men C or antibodies to the 7 *Streptococcus pneumoniae* serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-polio type 1 antibody titers ≥ 8
    - anti-polio type 2 antibody titers ≥ 8
    - anti-polio type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
    - anti-HBs antibody concentrations ≥ 10.0 mIU/ml
    - *Neisseria meningitidis* C serum bactericidal activity titer ≥ 1/8
    - ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 mcg/ml*** **(Amendment 1: 07 June 2005)**
    - antibody concentrations to *Streptococcus pneumoniae* serotypes 4, 9V,14, 18C, 23 F, 6B, 19F ≥ 0.05 mcg/ml
  - Seropositivity status:
    - anti-PT antibody concentrations ≥ 5 EL.U/ml
    - anti-FHA antibody concentrations ≥ 5 EL.U/ml
    - anti-PRN antibody concentrations ≥ 5 EL.U/ml

Safety and reactogenicity

- In a subset of subjects (N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccines.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccines, according to the MedDRA classification.

- For all subjects, occurrence of serious adverse events throughout the entire study period.

10.3. Estimated sample size

The primary objective of the study is to determine if two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations can prevent any RV GE caused by the circulating wild-type RV strains during the period starting from 2 weeks after Dose 2 of study vaccination until Visit 5 at the end of the first efficacy follow-up period.

3 990 subjects randomized to receive either the HRV vaccine or the placebo in a 2:1 ratio will be enrolled. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 3 390 subjects (2 260 in HRV and 1 130 in placebo groups respectively) are expected to be evaluable for the analysis of the primary objective.

Considering a 2:1 randomization ratio and various incidence rates, Table 12 provides the power that the 95% CI for vaccine efficacy be above given limits.

Results from a trial (Study 004) in Finland indicates that in placebo recipients an incidence rate of 10% for the percentage of subjects with any RV GE caused by the circulating wild-type RV strains from 2 weeks after Dose 2 of study vaccination up to Visit 5 at the end of the first efficacy follow-up period is a reasonable assumption.

Therefore if the vaccine efficacy is truly 70%, the study has at least 90% power to observe a 95% CI for the vaccine efficacy that will be above 50%.

Table 13 Power to observe a 95% CI above various cut-offs according to various incidence rates and true vaccine efficacy (power obtained from simulations using 2260 evaluable subjects in the HRV vaccine group and 1130 evaluable subjects in the placebo group) [see Appendix I for mathematical details]

Incidence rate in the placebo	True vaccine efficacy	Cut-off for the lower limit of the 95% CI on vaccine efficacy					
		0%	10%	20%	30%	40%	50%
Any Gastroenteritis							
10%*	70% 60%	100% 100%	100% 100%	100% 100%	100% 97%	100% 81%	91% 32%
8%	70% 60%	100% 100%	100% 100%	100% 99%	100% 94%	98% 73%	82% 29%
6%	70% 60%	100% 100%	100% 99%	100% 96%	99% 85%	93% 60%	71% 21%
Severe Gastroenteritis							
4%*	80% 70%	100% 100%	100% 99%	100% 98%	99% 93%	98% 81%	92% 53%
3%	80% 70%	100% 98%	99% 97%	99% 93%	97% 85%	93% 68%	80% 40%
2%	80% 70%	98% 92%	97% 86%	94% 78%	90% 64%	80% 46%	60% 26%

*anticipated incidence rate

A secondary objective is to explore the immunogenicity of the childhood vaccinations one month after the third dose of the primary vaccination course in each country. Two doses of the three-dose primary vaccination course would be co-administered with each dose of the HRV vaccine or placebo.

Using an estimation of the seroprotection rates of 97% for anti-diphtheria, of 99% for anti-tetanus, of 100% for anti-PRP, of 94% for anti-HBs, of 100% for anti-polio type 1, 2 and 3 antibodies and a standard deviation between 0.28 to 0.33 for anti-PT, anti-FHA, anti-PRN antibody concentrations (reference study: ROTA-007), and assuming that the rates / GMC are the same in the vaccine and placebo groups, a subset of 160 evaluable subjects in the vaccine group and 80 in the placebo group will provide at least 80% global power that all the 95% CIs on the decrease in seroprotection rates with the vaccine group as compared to the placebo group are below 10% and that the 95% CIs on the fold decrease in anti-PT, anti-FHA, anti-PRN GMCs with the vaccine group as compared to the placebo group is below 1.5 (using PASS 2000 for the difference in seroprotection rates and using Nquery for the ratio of anti-PT, anti-FHA, anti-PRN GMCs, one sided equivalence test, alpha=2.5%). These analyses will be exploratory.

Allowing for up to 20% of subjects who may not be evaluable for the immunogenicity analysis, a target total of 300 subjects will be sampled by country.

10.4. Study cohorts to be evaluated

Total Vaccinated cohort

The total vaccinated cohort will include all subjects with at least one vaccine administration documented:

- a safety analysis based on the total vaccinated cohort will include all vaccinated subjects,
- an immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects for whom immunogenicity data are available.
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available.

ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects:

- who received 2 doses of HRV vaccine or placebo,
- who have entered into the efficacy surveillance period:
  - have follow-up beyond 2 weeks after Dose 2 of study vaccination for the analysis of the first efficacy follow-up period,
  - have follow-up beyond the end of the first efficacy follow-up period for the analysis of the second efficacy follow-up period,

- have follow-up beyond 2 weeks after Dose 2 of study vaccination for analysis of the combined efficacy follow-up periods.

- for whom the randomization code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol

ATP cohort for safety

The ATP cohort for safety will include all vaccinated subjects

- who have received at least one dose of study vaccine/control according to their random assignment,
- for whom the randomization code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

ATP immunogenicity cohort

The ATP immunogenicity cohort will include all subjects from the ATP safety cohort:

- who have 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 comply with vaccination schedule for HRV vaccine or placebo,
- who comply with blood sampling schedule,
- for whom immunogenicity data are available, at pre and post sampling timepoint.
- who have no rotavirus other than vaccine strain in GE stool samples collected up to Visit 3.
- who have no concomitant infection unrelated to the vaccine which may influence the immune response.
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of dose 1. Refer to the glossary of terms for definition of seronegative.

The ATP efficacy cohort will be used for the primary analysis of efficacy. A secondary analysis of efficacy based on the total vaccinated cohort will also be performed.

The total vaccinated 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 ATP immunogenicity cohort will be used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort will only be performed if more than 5% of the enrolled subjects 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.

10.5. Derived and transformed data

Efficacy

An episode of GE will be classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain is identified in a stool sample collected during the episode. GE episode without stool sample/result available will not be considered in the analysis as a RV GE episode.

Reactogenicity

For a given dose, subjects with no symptoms (solicited or unsolicited) documented will be considered as subjects without symptoms (solicited or unsolicited).

Immunogenicity

The cut-off values of all antibodies are defined by the laboratory before the analysis and are described in Section 5.6.2.2.

A seronegative subject is a subject whose titer is below the cut-off value.

A seropositive subject is a subject whose titer is greater than or equal to the cut-off value.

Seroconversion is defined as the appearance of antibodies (i.e. titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination

The GMC calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

10.6. Final analyses

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed subsequently, and will be presented in an annex.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 5. However access to the individual treatment decode will be provided to the investigators only after the final analyses of the second efficacy follow-up be performed.

10.6.1. Analysis of demographics/baseline characteristics

The mean, range and standard deviation of height in cm, weight in kg and of age in weeks will be calculated per group. The racial and gender composition will be presented.

The distribution of subjects enrolled among the study centers will be tabulated as a whole and per group.

Summary of feeding criteria on the day of each study vaccination will be tabulated by group.

10.6.2. Analysis of efficacy

Vaccine efficacy will be calculated, with their 95% CI (see Appendix I for mathematical detail) against:

- any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any and severe RV GE due to G1 serotype caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any and severe RV GE due to non-G1 serotypes during the first efficacy follow-up period.
- hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any medical attention (medical provider contact, advice, visit; emergency room contact or visit; hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period for the subset of subjects who completed the two-dose vaccination course before the RV epidemic season.
- any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period for the subset of subjects who were vaccinated during the RV epidemic season.

The efficacy of the vaccine against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period will be first evaluated. The secondary efficacy objectives will be addressed using a hierarchical testing procedure according to the order listed above, provided that the primary efficacy objective has been reached.

In addition, vaccine efficacy against severe RV GE, severe RV GE due to G1 serotype, severe RV GE due to non-G1 serotypes, hospitalization due to RV GE and any medical attention for RV GE during the second efficacy period and on combined efficacy periods will be calculated, with their 95% CI.

Additional supportive and exploratory analyses will be performed (i.e. efficacy by country, efficacy against any RV GE during the second efficacy period, efficacy against

severe GE, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, efficacy against hospitalization due to GE of any etiology, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system and assessment of risk factors of RV infection).

10.6.3. Analysis of immunogenicity

In a subset of subjects (N=1800)

For each treatment group, at each time point that a given antigen is measured,

- Seropositivity/seroprotection /seroconversion rates and their exact 95% CI will be tabulated
- GMCs/GMTs and their 95% CI will be calculated.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 will be displayed using reverse cumulative curves.

The asymptotic standardized 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between vaccine and placebo groups will be computed.

In addition, for all childhood vaccinations co-administered with each study vaccine dose, the distribution of antibody titers after the second (if applicable) and one month after the third dose of the childhood vaccinations will be displayed, per country, using reverse cumulative curves.

Difference between vaccine and placebo groups after the second (if applicable) and one month after the third dose of the routine primary vaccination course will be evaluated per country with respect to immune response to the childhood vaccines:

- The asymptotic standardized two-sided 95% CI for difference in seropositivity/seroprotection rates between vaccine and placebo groups will be calculated.
- The two-sided 95% CI for the ratio of GMCs/GMTs between vaccine and placebo groups will be computed (using a one-way ANOVA model on the logarithm10 transformation of the titers).

10.6.4. Analysis of safety

In a subset of subjects (N=1800)

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 dose, for overall doses and per subject.

The incidence, with exact 95% CI, of each individual solicited general symptom, will be calculated by group, over the solicited follow-up period, after each dose, for all doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

An increase in the incidence of specific symptoms in HRV vaccine group as compared to placebo group will be explored using two-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 also be performed.

For all subjects

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA, the Medical Dictionary for Regulatory Activities. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited symptoms occurring within 31 days with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited symptoms with relationship to vaccination.

Serious adverse events reported during the study period will be summarized by group.

10.7. Planned interim analysis

(Amendment 1: 07 June 2005)

In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on subjects ***from the Czech Republic and Finland only*** from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data ***on solicited and unsolicited symptoms,*** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. ***No*** study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.

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

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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 fulfilment 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)

1. 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)

2. 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 and equipment 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 GSK Biologicals 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 ensure that no clinical samples (including serum samples) are retained on site or elsewhere without the approval of GSK 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 co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation; administrative changes are submitted to IRBs/IECs for information only.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such

action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to the investigational site.

V. Monitoring by GSK Biologicals

Monitoring visits by a professional representative of the sponsor will be scheduled to take place as close as possible to entry of the first subject, during the study at appropriate intervals and after the last subject has completed the study. It is anticipated that monitoring visits will occur at a frequency defined before study start.

These visits are for the purpose of confirming that GSK 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 accuracy of data entered on the RDE screens and Vaccine Inventory Forms. The monitor will verify 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 RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK 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 agencies and GSK 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, Biologics Licensing Application.

GSK Biologicals has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of vaccine development. GSK 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 GSK Biologicals sponsored studies are in accordance with GCP 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 GSK Biologicals' audits entail review of source documents supporting the adequacy and accuracy of eCRFs, review of documentation required to be maintained, and checks on vaccine accountability. The GSK Biologicals' audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK 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 consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of eCRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next

paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed Publication. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

APPENDIX C OVERVIEW OF THE RECRUITMENT PLAN

- The study will be conducted multiple sites in six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain).
- Target enrollment will be 3990 eligible subjects.
- A total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.
- Recruitment will be terminated when 3990 eligible subjects have been enrolled.
- All subjects will be enrolled within a period of 4 months.
- ***Recruitment was terminated on 31 January 31 2005.*** **(Amendment 1: 07 June 2005)**
- Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per subject, will not exceed a total of maximum of 24 months.
- The recruitment will be monitored by the site monitor / SBIR.

APPENDIX D HANDLING OF BIOLOGICAL SAMPLES COLLECTED BY THE INVESTIGATOR

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

3. 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 to minimize the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

4. Serum separation

These guidelines aim to ensure high quality serum by minimizing the risk of haemolysis, 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 ten 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 tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- 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 label provided by GSK Biologicals (see point 3).

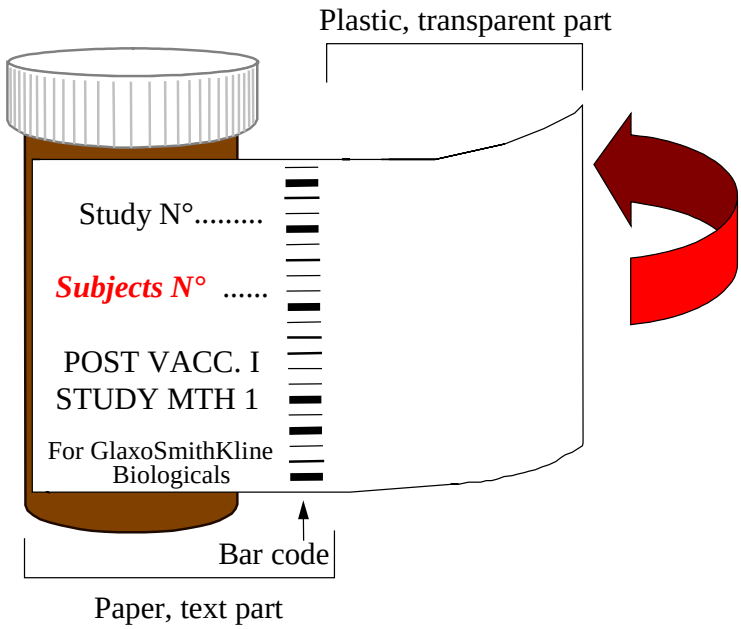
5. Labelling

- The standard labels provided by GSK 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.

(Amendment 1: 07 June 2005)



- Labels should not be attached to caps.

6. Sorting and storage

- Tubes should be placed in the GSK Biologicals' cardboard boxes 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 approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to GSK Biologicals. The storage temperature should be checked regularly and documented. Wherever possible, a backup facility for storage of serum samples should be available.
- A standard Serum Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. 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 serum samples.

- Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.[1]

GLAXOSMITHKLINE BIOLOGICALS

Attention Biospecimen Reception
Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart – Belgium
Telephone: [redacted] or [redacted]
or [redacted] or [redacted]
Fax: [redacted]
E-mail: [redacted]

Instructions for Handling of Stool Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

- Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any gastroenteritis episodes. Parents/guardians will be asked to preferably use the containers to collect stool samples. If this is not possible, soiled diapers should be individually placed in the ziplock bags and sealed.

2. Labelling

- The parents/guardians/study personnel should complete the label provided on the container/ziplock bag label with a black ink or ballpoint pen and return the collected stool samples to the study personnel.
- If necessary, any hand-written additions to the labels by the study personnel should be made using indelible ink.

3. Sorting and storage

[1] The Serum Listing Form and the Specimen Transfer Form are standard documents used in GSK Biologicals' clinical trials. These documents are provided by GSK Biologicals' Clinical Trials' monitor at study initiation.

- The 8 ml tubes with stool specimens should be stored at a temperature between -20°C and -70°C until shipment to GSK Biologicals. Wherever possible, a backup facility for storage of stool samples should be available
- A standard Stool Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. 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 serum samples.
- Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.[2]

Please refer to the GSK contact information mentioned above for serum samples.

Instructions for Handling of Biological Samples collected during IS

When materials are provided by GSK Biologicals, it is mandatory that all clinical samples (including serum samples) be collected and stored 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.

All biological specimens should be labelled to allow sample identification. If necessary, any hand-written additions to the labels should be made using indelible ink.

For samples to be tested locally at the investigator's laboratory

- Fresh stool samples should be maintained at the investigator's laboratory for testing for the presence of enteric pathogens such as Salmonella, Shigella, Campylobacter, E. coli and Yersinia.

For samples to be shipped to GSK Biologicals, Belgium

- The stool samples should be aliquoted in two samples, placed in 8 ml tubes and be kept at –20°C to –70°C. Rectal swabs and throat swabs should be placed in sterile transport media and frozen at –20°C to –70°C until shipment to GSK Biologicals. Acute and convalescent sera should be stored at –20°C until shipment to GSK Biologicals. If applicable, surgical specimens should be washed, stored and shipped according to the instructions in the lab workbook. Wherever possible, a backup facility for storage of stool samples should be available.

A standard Specimen Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. 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 stool samples.

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[2] The Stool Listing Form and the Specimen Transfer Form are standard documents used in GSK Biologicals' clinical trials. These documents are provided by GSK Biologicals' Clinical Trials' monitor at study initiation.

Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.

Please refer to the GSK contact information mentioned above for serum samples.

APPENDIX E SHIPMENT OF BIOLOGICAL SAMPLES

Instructions for Shipment of all Biological Samples

Biological samples should be sent to GSK Biologicals at regular intervals. The frequency of shipment of samples should be decided upon by the Site Monitor, Central Study Coordinator and the investigator prior to the study start.

Biological samples should always be sent by air, preferably on a Monday, Tuesday or Wednesday, unless otherwise requested by the sponsor.

Biological samples (except IS surgical samples) must be placed with dry ice (maximum -20°C) in a container complying with International Air Transport Association (IATA) requirements. The completed standard biological samples listing form should always accompany the shipment.

The container must be clearly identified with the labels provided by GSK Biologicals specifying the shipment address and the storage temperature (-20°C or 2-8°C for IS surgical samples).

The airway bill should contain the instruction for storage of samples at maximum -20°C or 2-8°C for IS surgical samples.

A "proforma" invoice, stating a value for customs purposes only, should be prepared and attached to the container. This document should contain the instruction for storage of samples at maximum -20°C or 2-8°C for IS surgical samples.

Details of the shipment, including:
* number of samples
* airway bill
* flight number
* flight departure and arrival times

should be sent by fax or by e-mail, two days before shipment, to:

GLAXOSMITHKLINE BIOLOGICALS
Attention Biospecimen Reception
Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart – Belgium
Telephone: [redacted] or [redacted]
or [redacted] or [redacted]
Fax: [redacted]
E-mail: [redacted]

APPENDIX F LABORATORY ASSAYS

Description of Clinical Immunological Assays

Measurement of IgA Antibodies by ELISA

This assay allows the detection of rotavirus IgA in human serum and was initially designed by R. Ward (1, 2) and has been adapted by GSK Biologicals. It will be used for measuring the immune response after vaccination and/or infection. Samples will be analyzed at GSK Biologicals, Rixensart, Belgium (or designated laboratory).

Description of the ELISA Assay

96-well plates are coated by overnight incubation with anti-rotavirus antibody dilutions. The wells are washed and a lysate of cells either infected with vaccine strain (positive wells) or either uninfected (negative wells) is added. Following incubation on a rotating platform, the plates are washed and the dilutions of serum samples or standard serum are incubated in both kinds of wells (positive and negative). The use of negative wells allows the assessment of non-specific IgA binding.

The plates are washed and bound human IgA is detected by addition of biotinylated rabbit anti-human IgA (30 minutes under agitation). After washing the plates, peroxidase-conjugated avidin-biotin at an optimal concentration is added to each well and incubated (30 minutes, RT under agitation). Plates are again washed and orthophenylenediamine (OPD) is added. The plates are then incubated (30 minutes, room temperature (RT) in darkness) before the reaction is stopped with 2N H2SO4.

Optical absorption is measured at 490/620 nm. Specific optical densities are calculated for each sample / standard by measuring the difference between positive and negative wells. Concentrations of the samples are determined by using the four-parameter logistic function generated by the standard curve. The most accurate part of the standard curve (working range) for the calculation of the results is determined. Antibody concentrations in units per milliliter (U/ml) are calculated 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 corrected for the dilution factor. Each experiment includes negative and positive controls.

For all reagents optimal concentration are pre-determined.

References

1. 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.

2. 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.

Stool assays

1. Antigen Detection in Stool Samples

Rotavirus antigen in stool samples collected during gastroenteritis episodes will be detected by ELISA at Central Lab (GSK or designated laboratory).

2. RV strain typing

Targeted RV gene will be amplified by Reverse Transcriptase Polymerase Reactions (RT-PCR) to generate RV cDNA fragments. The genotype will be confirmed by hybridization using serotype-specific DNA probes and/or by direct sequencing of the amplified RV cDNA product.

This serotyping analysis can be completed with the determination of the P-serotype which is related to the VP4 gene. In that case, the typing approaches will be based on the methods such as described for the G typing.

APPENDIX G VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY

1. Vaccine and/or other supplies

GSK Biologicals will supply the following amounts of numbered doses of study vaccine, sufficient to administer 2 dose(s) to all subjects as described in the present protocol.

- 5320 doses of the HRV vaccine in monodose vials.
- 2660 doses of the placebo in monodose vials.
- 7980 doses of the diluent (calcium carbonate buffer) pre-filled syringes.

An additional 5% of their respective amounts will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject). An additional quantity of vaccine stock not exceeding 20% of their respective amounts will be provided in order to allow over randomisation.

Commercially available lots will be provided for Infanrix Hexa®, Infanrix Polio Hib® and ***Prevenar*®** by GSK Biologicals, Rixensart, Belgium. **(Amendment 1: 07 June 2005)**

All monodose vials/pre-filled syringes must be accounted for on the form provided.

Labels for sample identification:
The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each timepoint. Each label will contain the following information: study number, identification number for the subject, sampling timepoint , timing , biological specimen (e.g. serum / GE stool).

Other supplies provided by GSK Biologicals:
In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:
For example:

- material for biological specimen during IS,
- material for blood collection,
- material for stool samples.

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers,

when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site

On arrival of vaccine shipment, the ***cold chain monitoring device*** should be removed from the vaccine boxes and checked. The temperature recording chart (chart from Cox recorder or print-out data of the electronic device) should be obtained from the temperature recording device. **(Amendment 1: 07 June 2005)**

The following documents should be completed and returned to GSK Biologicals on reception of vaccine shipment:

Notification of vaccine delivery/temperature control
Copy of the temperature recording (chart).

These documents should then be returned to:

(Amendment 1: 07 June 2005)

Attention of ***Clinical Trials Supply Unit***
Clinical Operations Logistics
GSK Biologicals Rixensart
Fax : [redacted]
E-mail: [redacted]

In case of any temperature deviation, the official approval for the use of vaccine must be obtained from GSK Biologicals.

4. Vaccine accountability

At all times 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 used and unused stocks. An explanation must be given of any discrepancies.

After approval from GSK Biologicals and in accordance with GSK SOP-WWD-1102, used and unused vaccine vials/syringes/containers should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine vials/syringes/containers are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK SOP-WWD-1102.

5. Transfers of clinical vaccines or products from country medical department or dispatch centre to study sites or between sites

Storage temperatures must be maintained during transport and deviations must be reported to Clinical Operations Logistics for guidance. All transfers of clinical vaccines or products must be documented using the Clinical Supply Transfer Form.

All packaging and shipment procedures for transfer of clinical vaccines or products must follow procedures approved by the sponsor.

Clinical vaccines or products should always be sent by contract courier designated by the sponsor, unless otherwise requested by the sponsor.

Alternative local validated procedures may be followed after the documentation for these procedures has been sent to Clinical Operations Logistics and approval has then been obtained from the qualified person (or designee) in GSK Biologicals, Rixensart, before any shipment of vaccines.

APPENDIX H 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 GSK Contact for Serious Adverse Event (SAE) Reporting.

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, collection date and process of serum, throat , stool and surgical specimen if any as well as any other information thought necessary for assessment by the study staff should be reported to the GSK safety contact by using the IS reporting form.

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 a range of suspected pathogens including Salmonella, Shigella, Campylobacter, and Yersinia. 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 GSK Biologicals, such as virus culture, antigen detection by immunoassay, or electron microscopy for virus-like particles. Accordingly, a complete set of stool specimens (collected just prior to or immediately after the air or contrast enema, 24 hours and 48 hours after the reduction) will be comprised of 3 specimens submitted for bacterial culture and 6 frozen specimens retained for shipment to GSK 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.

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.

In case of surgical resection, 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. As molecular assays are to be performed on these surgical specimens, the use of powderless gloves, RNAse-free pipettes, aerosol RNAse-free tips, non-autoclaved disposable plasticware/forceps, commercial PBS solution/ water/ formaldehyde solutions as well as limited steps of the solution preparation are highly recommended to avoid RNAse contamination. Refer to the lab workbook for the process of resected tissue. A broad range of tests including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR and other tests will be arranged by GSK Biologicals in consultation with the Attending Pathologist.

Acute and convalescent blood (at least 2 ml of each) should be collected. Serum should be 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 GSK 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 I MATHEMATICAL DETAILS ABOUT SAMPLE SIZE DETERMINATION SHEET

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{rn2}$$

where n1 = number of cases in the vaccine group

N1 = number of subjects in the vaccine group

n2 = number of cases in the placebo group

N2 = number of subjects in the placebo group

N1/N2 = r

*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 binomial 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 [redacted] and [redacted]

(Amendment 1: 07 June 2005)

APPENDIX J FRENCH ADMINISTRATIVE CONSIDERATIONS

This appendix includes all the requirements of the French law (n°88-1138 of 20 December 1988 modified), and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « STUDY POPULATION»

- ***In line with the local regulatory requirements, the following text about « NATIONAL FILE » is added :***

All subjects participating in studies could be identified and monitored under the « Fichier national ».

The following details will be described:

- ***first 3 letters of name and first 2 letters of surname,***
- ***date of birth,***
- ***reference of the study and dates of beginning and termination,***
- ***exclusion period,***
- ***the total amount of honorarium.***

- ***In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS » is added :***

A subject will be eligible for inclusion in this study if he /her is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

- ***In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS » is added :***

Subjects could be paid (if applicable) for the inconvenience of participating in the study. The amount of payment is stated in the informed consent form. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a <u>pro rata</u> basis.

2. Concerning the " DATA ANALYSIS AND STATISTICAL CONSIDERATIONS " and specially in the " SAMPLE SIZE ASSUMPTION "

The expected number of patients to be recruited in France is declared to the French regulatory authority and is included in the Patient Informed Consent Form.

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

- ***In section " Regulatory and Ethical Considerations, Including the Informed Consent Process"***
  - ***Concerning the process for informing the patient or his/her legally authorized representative, the following text is added :***

    French Patient Informed Consent form is a document in triplicate which summarizes the main features of the study and allows collection of the patient's written consent. It also contains a reference to the advice from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.

  - ***Concerning the process for obtaining subject informed consent,***

    If the patient is under 18 years old, the following text is added (if applicable):

    The consent of the child will be also sought when he/she is old enough to express his/her opinion. His/her refusal or the revocation of his/her consent cannot be disregarded. If only one holder of parental authority signed the consent form, the investigator will ask the present person to file, date and sign and affidavit (in triplicate) indicating wich his situation regarding the parental authority. A copy of this affidavit is joined to each consent form.

    If these directives are not followed, the patient inclusion could be considered as a protocol violation and the data of this case won't be taken into account.

  - ***Concerning the management of the Patient Informed Consent forms, the following text is added :***

    The first copy of the Patient Informed Consent form is kept by the Director of the Medical Department of GlaxoSmithKline France. The second copy is kept by the investigator and the last copy is given to the patient or his/her legally authorized representative.

    The first copy of all the consent forms will be collected by the investigator at the end of the trial under the Clinical Research Assistant's (CRA's) control, and placed in a sealed envelope bearing only :

    - ***the study number,***
    - ***the identification of the Centre : name of the principal investigator and number of center),***
    - ***the number of informed consents,***
    - ***the date,***
    - ***and the principal investigator's signing.***

Then, the CRA hands the sealed envelope over to the Director of the Medical Department, for confidential recording, under his responsibility.

- ***In section concerning the " NOTIFICATION TO THE HOSPITAL DIRECTOR " the following text is added (if applicable)***

In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.5121-17).

- ***In section concerning the " INFORMATION TO THE HOSPITAL PHARMACIST " the following text is added (if applicable)***

In accordance with Article R.5121-18 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- ***In section " RECORDS RETENTION "***

Concerning the documents to be retained by the Investigator is added :

The correspondance with the French Ethic committee must be filed only by the "Coordinating Investigator".

- ***In section " DATA MANAGEMENT " the following text is added***

" within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by Laboratoire GlaxoSmithKline or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through Laboratoire GlaxoSmithKline (Clinical Operations Department)."

" dans le cadre de cet essai clinique, les données concernant l'identité des investigateurs et/ou des co-investigateurs et/ou du pharmacien si applicable, participant à cet essai clinique, et les données concernant les patients recrutés dans cet essai clinique (numéro patient, numéro de traitement, statut du patient eu égard à l'essai clinique, dates de visites, données de santé) seront collectées et intégrées dans les bases de données GSK par Laboratoire GlaxoSmithKline ou pour son compte, pour le suivi, la gestion de l'essai clinique et l'utilisation des résultats de celle-ci. Conformément à la loi n° 78-17 du 6 janvier 1978 modifiée, chacune desdites personnes a un droit d'accès, de correction et d'opposition sur ses propres données par le biais de Laboratoire GlaxoSmithKline (département Opérations Cliniques)."

4. Concerning the « SAE »

In section " TRANSMISSION OF THE SAE REPORTS " :

The SAE Reports have to be transmitted to the GSK France Drug Safety Department, which name, address and phone number are :

Département de Pharmacovigilance

Laboratoire GlaxoSmithKline

100 Route de Versailles

78163 MARLY LE ROI

Tel : [redacted]

Fax : [redacted]

GlaxoSmithKline Biologicals
Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment date:	**Amendment 1 – 07 June 2005**
Coordinating author:	[redacted] Scientific Writer

Rationale/background for changes: This protocol was amended on **07 June 2005** for the following reasons:

- Specify measurement of anti Neisseria meningitidis antibody concentrations by ELISA for subset from Spain.
- Specify details of the reactogenicity interim analysis.
- To implement administrative changes (update SAE contact information, study contact information, sponsor information).
- Implement minor corrections/clarifications.

The following strikethrough and bolded italic text were amended:

Title page

Contributing authors [redacted] ~~Director~~

[redacted] ***Clinical Development Manager***

Sponsor signatory: [redacted] ~~Director~~

[redacted] ***Director***

Synopsis (Study design), Section 3 and Section 5.2

Finland: 3, 5, ***11***-12 months

- Study visits: Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 6).

  Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** ~~will~~ have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines.

Section 3

*At 7 months of age only for subjects from Spain ***(optional)***.
#At 12 months of age only for subjects from Italy ***(optional)***. At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" ***(optional)***.

Synopsis (Secondary Endpoints) and Section 10.2

- ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 mcg/ml***

Section 5.2

- In addition, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" (target N=300 per country) ~~will~~ ***may*** have ***if necessary*** an additional study visit because the blood sampling timepoint one month post Dose 3 of the childhood vaccines in these countries does not ***always*** coincide with study visits planned for all subjects.

Section 5.4 (Table 1)

Age **Visit** **Timing** **Sampling timepoint**	**6-14 weeks** **VISIT 1** **Day 0** **Pre**	**VISIT 2** **Month 1 or 2**	**VISIT 3** **Month 3 or 4** **Post vacc 2**	**VISIT 5**	**VISIT 7**
Physical examination	●	●	●‡		
Recording all childhood vaccinations	●	●	●	● ***Finland/Italy only***	
Record any concomitant medication/vaccination#	●	●	●	●	~~●~~

§Additional visits ***can be*** ~~are~~ planned ***if necessary*** for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset":

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 2)

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2*	VISIT 6 ITALY only Month 9 Post-vacc 2*	 FINLAND only Month 10 Post-vacc 2*
Physical examination	•‡	•‡	•‡

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 3)

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine schedule	3, 4, 5 months	3, 5, *11*-12 months	2, 3, 4 months	3, 5, 11 months	2, 4, 6 months

Section 5.5

Visit 4 is optional and may be combined with Visit 5.

Visit 6 is optional and may be combined with Visit 5.

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)***

Section 5.6.2.2

In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity ***and ELISA test***, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Table 5 Laboratory Assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	***In-house***	***mcg/ml***	***0.3***

Section 5.6.4

Table 6 Serology and Stool Analysis Plan

Serology					
Post-vacc 2*	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP, 7 *S. pneumoniae* serotypes (France and Germany only)	Immunogenicity subset ***except Spain*** (N=1~~5~~800)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), ~~serum bactericidal activity (Spain only),~~ D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	***3***	***HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)***	***N=300 from Spain***	***HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.***
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity ***and ELISA test***	N=300 from Spain	***Men C*** serum bactericidal activity ***and ELISA test***, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Section 6.1

GSK Biologicals' Infanrix Hexa®, Infanrix Polio Hib® ***and Prevenar®*** vaccines will be also supplied.

~~Prevenar® and Meningitec® if to be used during the study should be bought locally.~~

Section 6.3

All vaccines must be stored in a safe and locked place with no access for unauthorized personnel.

Vaccines will be stored at the defined range of temperature (i.e. +2 to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of temperature deviation (temperature outside the defined range, i.e. +2 to +8°C/ 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

proper functioning was demonstrated during the monitor's site evaluation,

if the system continues to work in case of a power failure, and

if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working when after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag®) close to the vaccines as a back up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C/ 36°F to 46°F), must be reported within 24 hours to the Sponsor (i.e. Study Monitor/ GSK Local Contact/ GSK Biologicals)

Following exposure to a temperature deviation, vaccines will not be used until written approval is given by the sponsor.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.

~~All vaccines 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/ 36°F to 46°F) and must not be frozen. Storage temperature should be monitored and documented at least once per day. Monitors will check the record chart at least once per month or after any out of range storage. It is advisable to have a back-up refrigerator/ freezer in case of power failure/ breakdown. Procedures must be in place to ensure that the vaccine is kept at the indicated temperature range at all times.~~

~~The study monitor must be contacted, as soon as possible, if the cold chain is broken (e.g. vaccines become frozen or refrigeration fails).~~

~~Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.~~

Section 8.8.2

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician ~~Dr~~ [redacted] Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [redacted] ***or*** [redacted]

Section 10.6.2

Additional supportive and exploratory analyses will be performed (i.e. efficacy by country, efficacy against any RV GE during the second efficacy period, efficacy against severe GE, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, efficacy against hospitalization due to GE of any etiology, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system and assessment of risk factors of RV infection).

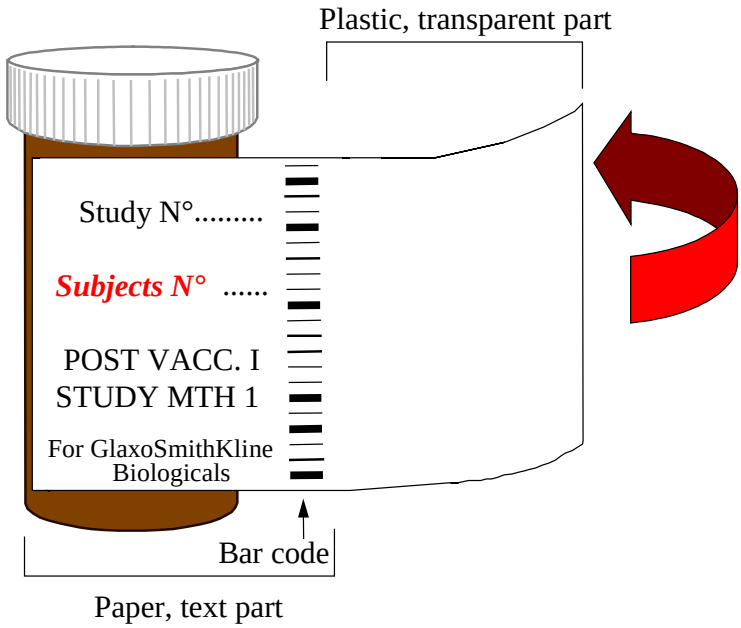
Section 10.7

In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on ~~all~~ subjects ***from the Czech Republic and Finland only*** from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data ***on solicited and unsolicited symptoms,*** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. ***No*** study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.

Appendix C

- Recruitment was terminated on 31 January 31 2005.

Appendix D



4. Collection

Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any ~~severe~~ gastroenteritis episodes.

Appendix G

Commercially available lots will be provided for Infanrix Hexa®, Infanrix Polio Hib® and ***Prevenar*®** by GSK Biologicals, Rixensart, Belgium.

~~Prevenar® and Meningitec® vaccines will be obtained locally.~~

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site

On arrival of vaccine shipment, the ~~freeze indicator~~ ***cold chain monitoring device*** should be removed from the vaccine boxes and checked ~~after 10 minutes at room temperature~~.

Attention of ***Clinical Trials Supply Unit*** [redacted]
E-mail: [redacted]

Appendix J

Appendix J FRENCH ADMINISTRATIVE CONSIDERATIONS was added.

Attachment 1 and Attachment 2

Study contact information and sponsor updated as appropriate.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Approved by: Director, Clinical Development	[redacted] dd-mm-yyyy

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	 _____ _____

Protocol Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Date of approval	Final 11 June 2004
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Sponsor signatory approval

Sponsor signatory: [redacted] Director

Signature: [redacted]

Date: 15 Jun 2004

Investigator Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine) and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investig

13 JUNE 2004

Date

Study 102247 (ROTA-036)

FILE NOTE – 15 March 2006

Concerns Original Final Protocol 11 June 2004 - Co-Investigators signatures pages
Amendment 1 - 07 June 2005 Co-Investigators signatures pages
CZEC REPUBLIC

- Study Protocol finalized 11-June-2004 was signed by Prof. [redacted] (Principal Investigator) on June, 23th 2004.
- Amendment 1 issued 07-June-2005 was signed by Prof. [redacted] (Principal Investigator) on July, 13th 2005.

The Co-Investigators did not sign the Final Protocol and the Amendment 1 as Prof. [redacted] was the Co-ordinating PI.

[redacted]
(Central Study Coordinator)

Date: 15 MAR 2006.

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Prof. [redacted]

[redacted] 22 June 2004

Investigator signature **Date**

Vesikari

NOTE TO FILE

Study: **102247 (rota-036 - Europe)**

Site #: **FINLAND** [redacted]

ITEM: **Signing of Final Protocol and Amendment #1**

Study 102247 (Rota-036 – Europe) study protocol was finalised 11-Jun-2004. Amendment #1 was issued 07-Jun-2005. At following centers in Finland there has been a change in the principal investigator (PI) between study start / final protocol (FP) and Amendment #1 (AM#1). Amendment #1 has been approved by local CA (National Agency for Medicines) on 28-Jul-2005. Following is to clarify the signing of the Protocol Investigator Agreement / Amendment approval pages at five centers:

[redacted](incl. sub-sites [redacted])
- former PI [redacted] end date: 19 Apr 2005 – has signed FP
- new PI [redacted] has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 03 Apr 2005 – has signed FP
- new PI [redacted] - has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 30 Jun 2005 – has signed FP
- new PI [redacted] - has signed AM#1

[redacted]
- former PI [redacted] end date: 30 Sep 2005 – has signed FP
- new PI [redacted] - has signed AM#1

[redacted]
- former PI [redacted] end date: 27 May 2005 – has signed FP
- new PI [redacted] - has signed FP and AM#1

Signature and date:

27 Jan 2006

[redacted]

[redacted]

Clinical Trials Manager
GlaxoSmithKline, Espoo, Finland

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 08 SEP 2009

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 06 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 09SEP2004

Investigator Signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

05-oct-04

[redacted] **signature** **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 02 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

04 may 2005

Date

#7985, 7986, 7987

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

[redacted]**vestigator signature**

6. SEP. 2004
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

09-SEP-2009

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 02 Sep 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 2.9.2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04 oct 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04 MAY 2005

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature 08 Sep 2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 09Sep2004

Investigator Signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 10SEP2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

17 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 13 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investi [redacted]

08.03.2004

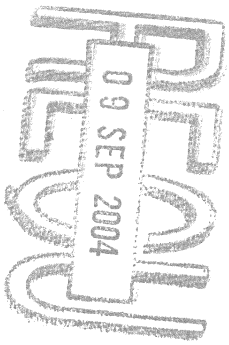
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

6-09-04

Investigator signature **Date**



P1 [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Co **Investigator name:** [redacted]

[redacted] 6-9-04

Investigator signature **Date**

Co [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signatu[redacted] **Date** 9.9.2004

[redacted]

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted]

Date 6 9 09

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted]

Date 9 Sep

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 11/10/04

Investigator si **Date**

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator [redacted] **Date** 150904

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 16/9/04

Investigator signature **Date**

[redacted]

[redacted]

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 06.09.04

Investigator signature **Date**

P1 # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted] MD

[redacted] 06/09/2004

Investigator signature **Date**

Co # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signa[redacted] 06 29 06

Date

P1 # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted]

Date 9/9/04

Co-th [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

04/09/09

Date

[redacted]

Co # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signatu [redacted]

4 September 2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted] **Date** 03 09 04

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 17.09.04

Investigator signature **Date**

France [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted] **tor signature** 13/09/04 **Date**

Pl# [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

16/09/2004

Date

Co # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted] **Date** 200904

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigato [redacted]

7/10/2004

Date

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

13 09 04

Investigator signature **Date**

[redacted]

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

Investigator signature [redacted]

29/09/04
Date

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Docteur [redacted]

Investigator signature **Date**

10-10-04.

[redacted]

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Docteur [redacted]

Investigator sig [redacted] **Date** 13/10/04

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted] **Date** 20 Nov 04

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted]

21.10.2004
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted] **Date** 26.10.04

PI # [redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22.09.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med. [redacted]

[redacted] 25. Aug. 04

Investigator signat [redacted] **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature [redacted] **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 07.10.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted] 25 AUG 2004

Investigator signatu **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: DR [redacted]

[redacted] 24. Sept. 04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 13.10.04

Inv[redacted] signature **Date**

[redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents

Investigator name: Dr. med. [redacted]

[redacted] 23.08.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 28.9.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: Dr. [redacted]

[redacted] 23.08.2004

Investigator signature **Date**

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"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

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Investigator name: Dr. [redacted]

[redacted] 23.8.04

Investigator **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: [redacted]

[redacted] 22.9.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Co ← **Investigator name:** [redacted]

[redacted] 23/06/04

Investigator signature **Date**

[redacted] 06/09/04

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]
Investigator signature

06/09/2004
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]
LKP signature

23.06.2004
Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: P ~~[redacted]~~

~~[redacted]~~ 26.8.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil ~~[redacted]~~

~~[redacted]~~ 23.06.2004

LKP signature **Date**

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] **Investigator signature**

28.08.2004
Date

[redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] **LKP signature**

23.06.2004
Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]
Investigator signature

25-Aug-2004
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted]
LKP signature

23.06.2004
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med. [redacted]

Dr. [redacted] 23. Aug. 2004

Investigator signature **Date**

Dr. med [redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 21.10.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investiga [redacted] 28.10.2004

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 12.09.04

Investigator signa **Date**

Dr med [redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
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Investigator name: [redacted]

[redacted] 22 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

01 FEB 2005

Date

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted] (for [redacted])

[redacted] 27.05.2005

Investigator signature **Date**

#7980

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 23804

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 23.05.07

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
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Investigator name: DR [redacted]

[redacted] 27 of OK

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
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Investigator name: [redacted]

[redacted] 29.08.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: Dr. med. [redacted]

[redacted]

Investigator signature

30 AUG 2004

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med [redacted]

[redacted]

Investigator signature

7/11/04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

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Investigator name: [redacted]

[redacted] 270804

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted]

Investigat

23108104

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 24.08.04

Investigator signature **Date**

[redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: [redacted]

[redacted] 23-09-2004

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: [redacted]

[redacted]

Investigator signature

Oct 8th 2004

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted] 28.5.04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med [redacted]

[redacted]

Investig

10. Okt. 2004
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

23.06.2004
Date

LKP signature

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04/11/2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 27/OCT/04

Investigator Signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

04 /NOV /2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted]

26/10/07
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 17/11/2009

Investigator signature **Date**

GlaxoSmithKline Biologicals Clinical Research & Development Protocol Amendment Approval	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment date:	**Amendment 1 – 07 June 2005**
Coordinating author:	[redacted] Scientific Writer

Rationale/background for changes: This protocol was amended on **07 June 2005** for the following reasons:

- Specify measurement of anti Neisseria meningitidis antibody concentrations by ELISA for subset from Spain.
- Specify details of the reactogenicity interim analysis.
- To implement administrative changes (update SAE contact information, study contact information, sponsor information).
- Implement minor corrections/clarifications.

The following strikethrough and bolded italic text were amended:

Title page

Contributing authors [redacted] ~~Director~~

[redacted] ***Clinical Development Manager***

Sponsor signatory: [redacted] ~~Director~~

[redacted] ***Director***

Synopsis (Study design), Section 3 and Section 5.2

Finland: 3, 5, ***11***-12 months

- Study visits: Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 6).

  Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** ~~will~~ have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines.

Section 3

*At 7 months of age only for subjects from Spain ***(optional)***.
#At 12 months of age only for subjects from Italy ***(optional)***. At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" ***(optional)***.

Synopsis (Secondary Endpoints) and Section 10.2

- ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 mcg/ml***

Section 5.2

- In addition, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" (target N=300 per country) ~~will~~ ***may*** have ***if necessary*** an additional study visit because the blood sampling timepoint one month post Dose 3 of the childhood vaccines in these countries does not ***always*** coincide with study visits planned for all subjects.

Section 5.4 (Table 1)

Age Visit Timing Sampling timepoint	6-14 weeks VISIT 1 Day 0 Pre	VISIT 2 Month 1 or 2	VISIT 3 Month 3 or 4 Post vacc 2	VISIT 5	VISIT 7
Physical examination	•	•	•‡		
Recording all childhood vaccinations	•	•	•	• *Finland/Italy only*	
Record any concomitant medication/vaccination#	•	•	•	•	•

§Additional visits ***can be*** ~~are~~ planned ***if necessary*** for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset":

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 2)

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2*	VISIT 6 ITALY only Month 9 Post-vacc 2*	 FINLAND only Month 10 Post-vacc 2*
Physical examination	•‡	•‡	•‡

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 3)

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine schedule	3, 4, 5 months	3, 5, *11*-12 months	2, 3, 4 months	3, 5, 11 months	2, 4, 6 months

Section 5.5

Visit 4 is optional and may be combined with Visit 5.

Visit 6 is optional and may be combined with Visit 5.

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)***

Section 5.6.2.2

In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity ***and ELISA test***, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Table 5 Laboratory Assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	***In-house***	***mcg/ml***	***0.3***

Section 5.6.4

Table 6 Serology and Stool Analysis Plan

Serology					
Post-vacc 2*	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP, 7 *S. pneumoniae* serotypes (France and Germany only)	Immunogenicity subset ***except Spain*** (N=15~~8~~00)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), ~~serum bactericidal activity (Spain only),~~ D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	***3***	***HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)***	***N=300 from Spain***	***HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.***
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity ***and ELISA test***	N=300 from Spain	***Men C*** serum bactericidal activity ***and ELISA test***, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Section 6.1

GSK Biologicals' Infanrix Hexa®, Infanrix Polio Hib® ***and Prevenar®*** vaccines will be also supplied.

~~Prevenar® and Meningitec® if to be used during the study should be bought locally.~~

Section 6.3

All vaccines must be stored in a safe and locked place with no access for unauthorized personnel.

Vaccines will be stored at the defined range of temperature (i.e. +2 to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of temperature deviation (temperature outside the defined range, i.e. +2 to +8°C/ 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

proper functioning was demonstrated during the monitor's site evaluation,

if the system continues to work in case of a power failure, and

if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working when after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag®) close to the vaccines as a back up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C/ 36°F to 46°F), must be reported within 24 hours to the Sponsor (i.e. Study Monitor/ GSK Local Contact/ GSK Biologicals)

Following exposure to a temperature deviation, vaccines will not be used until written approval is given by the sponsor.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.

~~All vaccines 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/ 36°F to 46°F) and must not be frozen. Storage temperature should be monitored and documented at least once per day. Monitors will check the record chart at least once per month or after any out of range storage. It is advisable to have a back-up refrigerator/ freezer in case of power failure/ breakdown. Procedures must be in place to ensure that the vaccine is kept at the indicated temperature range at all times.~~

~~The study monitor must be contacted, as soon as possible, if the cold chain is broken (e.g. vaccines become frozen or refrigeration fails).~~

~~Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.~~

Section 8.8.2

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician ~~Dr~~ [redacted] Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability [redacted] ***or*** [redacted]

Section 10.6.2

Additional supportive and exploratory analyses will be performed (i.e. efficacy by country, efficacy against any RV GE during the second efficacy period, efficacy against severe GE, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, efficacy against hospitalization due to GE of any etiology, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system and assessment of risk factors of RV infection).

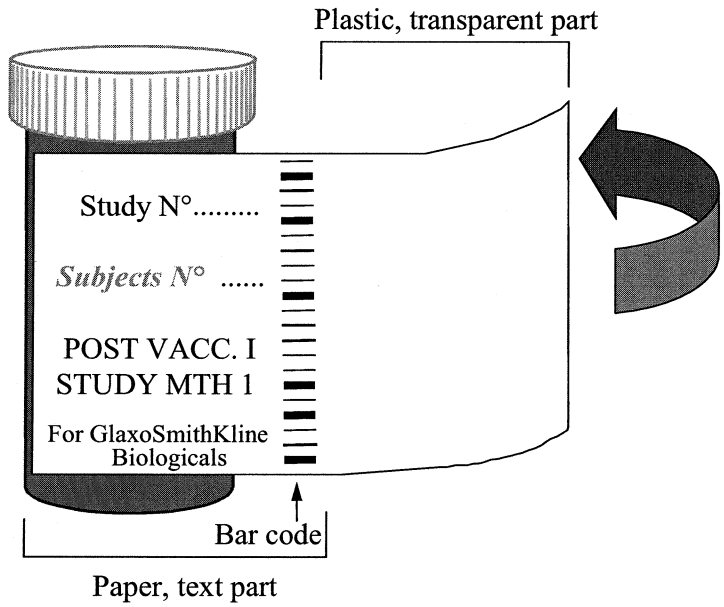
Section 10.7

In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on ~~all~~ subjects ***from the Czech Republic and Finland only*** from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data ***on solicited and unsolicited symptoms,*** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. ***No*** study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.

Appendix C

- Recruitment was terminated on 31 January 31 2005.

Appendix D



4. Collection

Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any ~~severe~~ gastroenteritis episodes.

Appendix G

Commercially available lots will be provided for Infanrix Hexa®, Infanrix Polio Hib® and ***Prevenar®*** by GSK Biologicals, Rixensart, Belgium.

~~Prevenar® and Meningitec® vaccines will be obtained locally.~~

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site

On arrival of vaccine shipment, the ~~freeze indicator~~ ***cold chain monitoring device*** should be removed from the vaccine boxes and checked ~~after 10 minutes at room temperature~~.

Attention of ***Clinical Trials Supply Unit*** ~~Stephanie Nitelet~~
E-mail: [redacted]

Appendix J

Appendix J FRENCH ADMINISTRATIVE CONSIDERATIONS was added.

Attachment 1 and Attachment 2

Study contact information and sponsor updated as appropriate.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Approved by: Director, Clinical Development	[redacted] 09-06-2005 dd-mm-yyyy

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 13 JUL 2005

[redacted]
CZEC REP.

Study 102247 (ROTA-036)

FILE NOTE – 15 March 2006

Concerns Original Final Protocol 11 June 2004 - Co-Investigators signatures pages
Amendment 1 - 07 June 2005 Co-Investigators signatures pages
CZEC REPUBLIC

- Study Protocol finalized 11-June-2004 was signed by Prof. [redacted] Principal Investigator) on June, 23th 2004.
- Amendment 1 issued 07-June-2005 was signed by Prof. [redacted] (Principal Investigator) on July, 13th 2005.

The Co-Investigators did not sign the Final Protocol and the Amendment 1 as Prof. [redacted] was the Co-ordinating PI.

[redacted]
(Central Study Coordinator)

Date: 15 MAR 2006.

GlaxoSmithKline Biologicals Clinical Research & Development **_ Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 7 July 2005

Co-Ordinating Unit

[redacted]

NOTE TO FILE

Study: **102247 (rota-036 - Europe)**

Site #: **FINLAND** [redacted]

ITEM: **Signing of Final Protocol and Amendment #1**

Study 102247 (Rota-036 – Europe) study protocol was finalised 11-Jun-2004. Amendment #1 was issued 07-Jun-2005. At following centers in Finland there has been a change in the principal investigator (PI) between study start / final protocol (FP) and Amendment #1 (AM#1). Amendment #1 has been approved by local CA (National Agency for Medicines) on 28-Jul-2005. Following is to clarify the signing of the Protocol Investigator Agreement / Amendment approval pages at five centers:

[redacted] (incl. sub-sites [redacted])
- former PI [redacted] end date: 19 Apr 2005 – has signed FP
- new PI [redacted] has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 03 Apr 2005 – has signed FP
- new PI [redacted] has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 30 Jun 2005 – has signed FP
- new PI [redacted] has signed AM#1

[redacted]
- former PI [redacted] end date: 30 Sep 2005 – has signed FP
- new PI [redacted] has signed AM#1

[redacted]
- former PI [redacted] end date: 27 May 2005 – has signed FP
- new PI [redacted] has signed FP and AM#1

Signature and date:

27 Jan 2006

[redacted]

[redacted]

Clinical Trials Manager
GlaxoSmithKline, Espoo, Finland

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	18 AUG 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 22-Aug-2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 31 MAY 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	28 Sep 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	12 SEP 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 19/Aug/2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	
Investigator signature:	[redacted]
Date:	29 Aug 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	25-AUG-2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] 13 Oct 2005 [redacted] Oct 07 June 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	05 Sep 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	19 aug 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	30 AUG 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] 25 AUG 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted] 13 Oct 2005
Date:	07 ~~June~~ Oct 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 27 Sep 2005

Center [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 27SEP2005

[redacted]

JARVENPÄÄ

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 13 Oct 2005 07 Oct 2005

[redacted]

Coutre [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 21.11.2005

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102247
Final

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 25.01.06

[redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by:	
Investigator:	[redacted]
Investigator signature:	
Date:	26.1.06.

[redacted]

Centre n° [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 Europe
EudraCT number	2004-001125-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator:	[redacted]
Investigator signature	[redacted]
Date:	27/7/05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator:	[redacted]
Investigator signature:	[redacted]
Date:	14 10 05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 10/10/05

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator:	[redacted]
Investigator signature:	[redacted]
Date:	25 01 2006

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 14/10/05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	8. 10. 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 17/10/05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 060106

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	[redacted]
Date:	07.10.2005

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	09/12/05

CONFIDENTIAL 102247
Final

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Docteur [redacted] 27 01 06

Study 102247 (ROTA-036)

FILE NOTE – 16 March 2006

Concerns Original Protocol AM1 (07/June/04) Investigator Approval Page 9 – **France Investigator N° [redacted] (Dr. [redacted]**

- Quality of the copy of signature page for Principal Investigator N° [redacted] received at Rixensart at this time is poor but I hereby confirm that the Protocol Amendment 1 Summary & Approval Form has been signed by Dr. [redacted] on 26/Jan/06.

[redacted]
(Central Study Coordinator)

Date: 16/03/2006

D1 [redacted]
Centre n° [redacted]

CONFIDENTIAL 102247
Final

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 26/1/06

[redacted] [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 08/10/2005

[redacted]

[redacted]

CONFIDENTIAL

102247
Final

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102247
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EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005

Agreed by:
Investigator:

Investigator signature:

Date:

[redacted]

[redacted]

30/11/06

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator:	[redacted]
Investigator signature:	[redacted] Docteur [redacted]
Date:	7-10-05

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator	[redacted]
Investigator signature:	[redacted]
Date:	17/10/05

Study 102247 (ROTA-036)

FILE NOTE – 15 March 2006

Concerns Original Protocol AM1 (07/June/04) Investigator Approval Page 9 – **France Investigator N°** [redacted] **(Dr.** [redacted]

- Quality of the copy of signature page for Principal Investigator N° [redacted] received at Rixensart at this time is poor but I hereby confirm that the Protocol Amendment 1 Summary & Approval Form has been signed by Dr. [redacted] on 24/Jan/06.

[redacted]
(Central Study Coordinator)

Date: 16/3/06

[redacted]

CONFIDENTIAL

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	[redacted]
eTrack abbreviated title	[redacted]
EudraCT number	[redacted]
Protocol title:	[redacted]
Amendment number:	Amendment 1
Amendment date:	[redacted]

Agreed by:
Investigator: [redacted]

Investigator signature:

Date: 24 01 06

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	21-10-05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr [redacted] [redacted] 27.07.2005

(GER) PI #7712

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	20. JULY. 2005

(GER)P1 # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator:	Dr [redacted]
Investigator signature:	[redacted]
Date:	27 Sept 2005

(Ger) P1 [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	DR [redacted] 21. July 2005

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signatur** **Date:**	[redacted] 25.07 [redacted]

center [redacted]

[redacted]

Dr. [redacted]

center (GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	25 JUL 2005

(GER)P1 # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. med. [redacted] [redacted] 04.08.2005

(GER) PI # [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr [redacted] In [redacted] 21 JULY 2005

(GER) PI # [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 29-7-05

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	[redacted]
Date:	20 Jul 2005

[redacted]

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Prof. [redacted]
Investigator signature:	[redacted]
Date:	21.8.05

(GER) PI# [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] 20-Jun-2005

(Ger) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Investigator:	Dr [redacted]
Investigator signature:	Dr. [redacted]
Date:	20. Jul. 2005

(GER) PI # [redacted]

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102247
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EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	[redacted]
Date:	15.6.05

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	01-JUL-2005

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	20. Juli 2005

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 20.7.05

(GER) PI #[redacted]

GlaxoSmithKline Biologicals

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Dr [redacted] **Investigator:** **Investigator signature:**	[redacted]
Date:	20.07.01

(GER) PI# [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
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EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr [redacted] [redacted] 29 Jul 2005

center [redacted]

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

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eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] [redacted] 21 JUL 2005

(GER) # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 18 09 05

(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 19/07/05

center [redacted]
(GER) PI # [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] [redacted] 1.8.05

(GER) P1 # [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	[redacted]
Date:	10-AUG-2005

(GER) [redacted] # P1

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: [redacted]	
Investigator:	
Investigator signature:	[redacted]
Date:	22.5.05

16. MAR. 2006 15:34 GSK [redacted] NR. 6848 S. 1

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	[redacted]
Date:	11-Aug-2005

(GER) PI # [redacted]

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted] 29/07/2005

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

GlaxoSmithKline File Note

INVESTIGATIONAL PRODUCT (ASSET) NAME/ NUMBER	STUDY IDENTIFIER	INVESTIGATOR NAME	CENTER NUMBER
Human Rotavirus Vaccine (444563)	102247 (ROTA-036)	Prof. [redacted]	[redacted]

Details:

This file note is intended to testify that Prof. [redacted] signed only page 4 (Investigator Agreement) for amendment n.1 of protocol Rota-036. The "Summary and Approval Page" has not been signed and will be signed secondly.

Author's Name (Print): [redacted]

Signature of Author:

Date Written: 16th March 2006

GlaxoSmithKline File Note

INVESTIGATIONAL PRODUCT (ASSET) NAME/ NUMBER	STUDY IDENTIFIER	INVESTIGATOR NAME	CENTER NUMBER
Human Rotavirus Vaccine (444563)	102247 (ROTA-036)	Prof. [redacted]	[redacted]

Details:

This file note is intended to testify that Prof. [redacted] signed only page 4 (Investigator Agreement) for amendment n.1 of protocol Rota-036. The "Summary and Approval Page" has not been signed and will be signed secondly.
Amend # 1 Investigator Agreement page 4 will be sent directly from the site to Rixensart (Attn. [redacted] by end of w/c 13th March 2006.

Author's Name (Print): [redacted]

Signature of Author:

Date Written: 16th March 2006

TITLE: ROTA-036/102247 Summary of Change Signature page Spanish PIs
DATE: 01-mar-06
BY: Monitor...
"This file note is to document that the investigators listed below who participate in study 102247/ROTA-036 in Spain were only requested to sign page 4 of the protocol Amndment 1 (07June2005) and not page 9 of the "Summary of changes of Amendment 1 section. Therefore there is no possibility to archive the original of pages 9 of the "Summary of changes of Amendment 1 for the Spanish Investigators"
Please add a table with all center number, PI last and first names, date at wich the PI signed AM1.

Center #	PI Last name	PI first name	AM1 pg 4 signed date
[redacted]	[redacted]	Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dr [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005

[redacted]

Signed by: [redacted] Date: 01-Mar-2006
Study Monitor

Study 102247 (ROTA-036)

FILE NOTE – 16 March 2006

Concerns Amendment 1 - 07 June 2005 Investigators signatures pages SPAIN

- Approval page 4 of the Amendment 1 was signed (on 01-Aug-2005) by Dr [redacted] (Principal Investigator-center 8256), replacing former Principal Investigator Dr. [redacted] who retired from study Rota-036.
- Like the other Investigators of the Spanish centers for the study Rota-036, he was not requested to sign page 9 of the "Summary of changes".

[redacted]
(Central Study Coordinator)

Date: 16/03/06

NOTE TO THE FILE. Rota-036 Study (102247)

Please note that Dr. [redacted] Principal Investigator from [redacted] – centre [redacted] has been retired from the study Rota-036. This point was reported to the Spanish Minister of Health on the 29th of July 2005.

[redacted]

DATE : 29/JUL/2005

[redacted]
Clinical Reasearch Associate

Sample CRF

Workbook

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Treatment number

|__|__|__|__|__|

Protocol 102247 (Rota-036)

A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

GENERAL INSTRUCTIONS

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.

DATES

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

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 **Study Conclusion** form**.**

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
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

One or more episodes of forceful emptying of partially digested stomach contents $\geq$ 1 hour after feeding within a day

Diarrhea
Passage of three or more looser than normal stools (loose or watery stools), within a day

GASTROENTERITIS EPISODES
Diarrhea with or without vomiting.

INTENSITY FOR NON-SOLICITED SYMPTOMS
1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: 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 attention).

ADVERSE EVENT DEFINITIONS

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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 / Resolved

2: Recovering / Resolving: If the subject is recovering at the time the subject completes the study or at the time the subject dropped out

3: Not recovered / Not resolved: This means an AE ongoing at the time the subject completes the study or becomes lost to follow-up; if AE/SAE was ongoing at the time of death, but was not the cause of death.

4: Recovered with sequelae / Resolved with sequelae

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
prolongation of existing hospitalization
is a congenital anomaly / birth defect in the offspring of a study subject

In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours.

GlaxoSmithKline Biologicals

102247 (Rota-036)

FLOW SHEET

Age Visit § Timing Sampling timepoint	6-14 weeks VISIT 1 Day 0 Pre	VISIT 2 Month 1 or 2	VISIT 3 Month 3 or 4 Post vacc 2	VISIT 5	VISIT 7
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in a subset: for antibody determination	● (1 ml) (N=1800)		● (3 ml) (N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations∗	●	●			
Recording all childhood vaccinations	●	●	●		
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)	●	●			
Return of reactogenicity diary cards in a subset (N=1800)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination	●	●	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●
Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

§Additional visits are planned for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset": Visit 4 will take place in Spain only and Visit 6 take place in Finland and Italy only. Visit 4 and Visit 6 are not applicable for France, Germany and the Czech Republic. Refer to Table 2 for more details.

Note: The double-line border following Month 3 indicates the interim analysis which will be performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗ The third dose of the routine childhood vaccine(s) must be given according to the respective national Immunisation plans of each country. A study visit is not planned specifically for administration of third dose of the routine childhood vaccine(s).

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

GlaxoSmithKline Biologicals

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FLOW SHEET (continued)

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2∗	VISIT 6 ITALY only Month 9 Post-vacc 2∗	VISIT 6 FINLAND only Month 10 Post-vacc 2∗
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●	●	●
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in a subset: for antibody determination (3 ml)	● (target N=300 from Spain)	● (target N=300 from Italy)	● (target N=300 from Finland)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)			
Return of reactogenicity diary cards in a subset (N=1800)			
Transcription of the reactogenicity diary card in a subset (N=1800)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of routine childhood vaccinations.

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

GlaxoSmithKline Biologicals

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FLOW SHEET (continued)

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject's evaluability in the according to protocol analyses.
The local national Plan of Immunization schedules vary from country to country. The local immunization schedule should be followed to administer study vaccine concomitantly with specific childhood vaccinations at Visit 1 and Visit 2. In order to assess the safety of the study vaccine, the interval between two study vaccine doses should not be less than 30 days. Table 1 presents the interval between study visits to be followed in each specified country. Table 2 presents the age at each visit per country.

Table 1 Intervals between study visits

Interval	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Routine schedule	**3, 4, 5 months**	**3, 5, 12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccines
End of the 1st efficacy follow-up period	mid-June to end-July 2005				
one month after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable
End of the 2nd efficacy follow-up period	mid-June to end-July 2006				

Table 2 Age of the subjects at each study visits

Age at Visit	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Visit 1	3 months	3 months	2 months	3 months	2 months
Visit 2	4 months	5 months	3 months	5 months	4 months
Visit 3	6 months	6 months	5 months	6 months	6 months
Visit 4	Not applicable				7 months
Visit 5	Will vary (Visit to be completed by mid-June to end-July 2005)				
Visit 6	Not applicable	13 months	Not applicable	12 months	Not applicable
Visit 7	Will vary (Visit to be completed by mid-June to end-July 2006)				

VISIT 1

DAY 0

DOSE 1

Informed Consent has to be obtained prior to any study procedure

GlaxoSmithKline Biologicals

Protocol

102247 (Rota-036)

ELIMINATION CRITERIA DURING THE STUDY

- *The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol analysis.*

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)

[C] Administration of a vaccine 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.

[D] Administration of immunoglobulins and/or any blood products during the study period.

[E] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

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Protocol

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CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

GSK Biologicals' HRV vaccine or placebo:
The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine 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 AE.

[F] Hypersensitivity reaction due to the vaccine.

[G] IS.

The following AEs constitute contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs 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 AE.

[H] Axillary temperature ≥ 37.5°C or rectal temperature ≥ 38.0°C..

[I] GE within 7 days preceding the study vaccine administration.

Co-administered vaccines:
For detailed information on Infanrix Hexa®, Infanrix Polio Hib®, *Neisseria meningitidis* C vaccine (e.g. Meningitec®) and *Streptococcus pneumoniae* vaccine (e.g. Prevenar®) to be co-administered with HRV vaccine or placebo, please consult the summary of product characteristics of the respective product in each country.

DTP vaccines (including Infanrix Hexa® and Infanrix Polio Hib®)
The following AEs constitute absolute contraindications to further administration of DTP vaccine; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine 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 AE:
Absolute contra-indications:

[J] Hypersensitivity reaction due to the vaccine.

[K] Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.

The following AEs constitute contraindications to administration of the study vaccine at that point in time; if any one of these AEs 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 AE.

[L] Acute disease at the time of vaccination. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).

[M] Axillary temperature ≥37.5°C (99.5°F) / Rectal temperature ≥38°C (100.4°F) / Oral temperature ≥37.5°C (99.5°F).

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Protocol

102247 (Rota-036)

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION (cont)

Precautions:

[N] Fever of ≥40.5°C (rectal temperature) or ≥40.0°C (axillary temperature) within 48 hours of vaccination not due to another identifiable cause.

[O] Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.

[P] Persistent, inconsolable crying occurring within 48 hours of vaccination and lasting ≥ 3 hours.

[Q] Seizures with or without fever occurring within 3 days of vaccination.

Meningitec®
Absolute contraindications include:

[R] Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

[S] Acute severe febrile illness.

Prevenar®
Absolute contraindications include:

[T] Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

[U] Acute severe febrile illness.

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|___|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Center number : |__|__|__|__|__|__|

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender :
[M] ☐ Male
[F] ☐ Female

Race :
[1] ☐ Black
[4] ☐ Arabic/North African
[2] ☐ White/Caucasian
[5] ☐ East & South East Asian
[6] ☐ South Asian
[7] ☐ American Hispanic
[8] ☐ Japanese
[9] ☐ Other, please specify : _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

1.

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102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|_____|

ELIGIBILITY CHECK

Did the subject meet all the entry criteria ?

☐ Yes ☐ No → If No, tick (✓) all boxes corresponding to violations of any inclusion/exclusion criteria.

Do not enter the subject into the study if he/she failed any inclusion or exclusion criteria below.

INCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the inclusion criteria the subject failed

[1] ☐ Subjects who the investigator believes that their parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits, collection of stool samples) should be enrolled in the study.

[2] ☐ A male or female between, and including, 6 and 14 weeks (42 – 104 days) of age at the time of the first vaccination.

[3] ☐ Written informed consent obtained from the parent or guardian of the subject.

[4] ☐ Free of obvious health problems as established by medical history and clinical examination before entering into the study.

[5] ☐ Birth weight > 2000g.

EXCLUSION CRITERIA

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.

[8] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)

[9] ☐ History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B disease (in all subjects). Only for subjects in Spain: history of meningococcal group C disease. Only for subjects in France and Germany: history of disease caused by *Streptococcus pneumoniae*.

[10] ☐ History of use of experimental rotavirus vaccine.

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Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|_____|

ELIGIBILITY CHECK

EXCLUSION CRITERIA (continued)

[11] ☐ Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (in all subjects). Only for subjects in Spain: previous vaccination against meningococcal group C. Only for subjects in France and Germany: previous vaccination against *Streptococcus pneumoniae*.

[12] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract, IS or other medical condition determined to be serious by the investigator.

[13] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

[14] ☐ History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

[15] ☐ Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).)

[16] ☐ Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).

[17] ☐ A family history of congenital or hereditary immunodeficiency.

[18] ☐ Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.

[19] ☐ History of any neurologic disorders or seizures.

[20] ☐ Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number |__|__|__|__|__|

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Protocol	CRF	Visit		Subject Number
102247	|___|	**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 tick (✓) appropriate box(es) and give diagnosis.

	DIAGNOSIS		PAST	CURRENT
[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]	**Muskuloskeletal**	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.

4.

Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|_____|

LABORATORY TESTS

BLOOD SAMPLE (in a subset for Finland)

Has a blood sample been taken ?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

☐ NA

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

EPIDEMIOLOGICAL DATA

Number of siblings : |_____|

Attendance to day care center : ☐ Yes
☐ No

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Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__|°C → Route : [A] ☐ Axillary
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or Placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

Comments : _____

(*) Why not administered ?

Please tick the **ONE most appropriate** category for non administration :

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N° : |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N°: |__|__| or Solicited AE code : |__|__|

☐ [OTH] Other, please specify : _____
(e.g. : consent withdrawal, protocol violation, …)

Please tick who took the decision : [I] ☐ Investigator [P] ☐ Parents/Guardians

If regurgitation or vomiting occurs after vaccination, no additional HRV vaccine/placebo dose should be administered at this visit.

IMMEDIATE POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time (30 minutes) please fill in the **Solicited Adverse Events** section**,** the **Non-Serious Adverse Event** section or a **Serious Adverse Event** form**.**

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box**.**

6.

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|_____|

CONCOMITANT VACCINE ADMINISTRATION

Infanrix hexa

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year

Meningitec (Spain only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year
☐ NA

Prevenar (France & Germany only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year
☐ NA

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

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Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 1**		|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

Has the subject experienced any of the following signs/symptoms including diarrhea during the solicited period?

[91] ☐ Information not available
[92] ☐ No vaccine administered
[0] ☐ No
[1] ☐ Yes, please **tick** No/Yes **for each symptom.** If Yes is ticked, please **complete** all items.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?	Date of last day of symptoms day month year	Causa-lity?	Medical attention
Fever (FE) ☐ No ☐ Yes → °C : [A] ☐ Axillary [R] ☐ Rectal	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Cough / Runny nose (CO) ☐ No ☐ Yes → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Irritability/ Fussiness (IR) ☐ No ☐ Yes → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Loss of appetite (LO) ☐ No ☐ Yes → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Vomiting (VO) ☐ No ☐ Yes → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|

Intensity:
0
1
2
3

Fever: Axillary ≥ 37.5°C
Rectal ≥ 38°C

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

If any of these **adverse events** are **serious** according to Protocol definition, please report event to GSK monitor by telephone or fax within 24 hours (see Protocol) and complete the **Serious Adverse Event form**.

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Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 1**		|__|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?	Causa-lity?	Medical attention
Diarrhea (DA)(*) ☐ No ☐ Yes (**) → number of looser than normal stools:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→ please fill the GE section	☐ No ☐ Yes	☐ No ☐ Yes→ HO/ER/MD/AD |__|__|

(*) Stool sample should be collected in case of diarrhea.

Stool collection date : |__|__| |__|__|__| |__|__|__|__| Hour : |__|__| |__|__|
day month year hours min

Stool collection date : |__|__| |__|__|__| |__|__|__|__| Hour : |__|__| |__|__|
day month year hours min

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

(**) If diarrhea yes, please complete the following items.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Irritability/less playfull	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for diarrhea :

☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|__|__|__|__|__|__|__|

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination ?

[91] ☐ Information not available

[92] ☐ No Vaccine administered

[0] ☐ No

[1] ☐ Yes, fill in the Non-Serious Adverse Event pages or Serious Adverse Event form.

10.

VISIT 2

MONTH 1 or 2

Dose 2

30 – 48 days after Visit 1 for Czech Republic, France and Germany

49 – 83 days after Visit 1 for Finland, Italy and Spain

REMINDERS

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.

ADVERSE EVENTS

Please report adverse events as specified in the Protocol and fill in the **Non-Serious Adverse Events** pages or the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa, Infanrix PolioHib, Prevenar and Meningitec in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 2**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 2 ?

☐ Yes, please complete the next pages.
☐ No

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify : _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision : [I] ☐ Investigator [P] ☐ Parents/Guardians

11.

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|___|	**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from one week after dose 1 until visit 2?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**
→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes
☐ No

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__|°C → Route : [A] ☐ Axillary
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or Placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

Comments : _____

(*) Why not administered ?

Please tick the **ONE most appropriate** category for non administration :

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N° : |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N°: |__|__| or Solicited AE code : |__|__|

☐ [OTH] Other, please specify : _____
(e.g. : consent withdrawal, protocol violation, …)

Please tick who took the decision : [I] ☐ Investigator [P] ☐ Parents/Guardians

If regurgitation or vomiting occurs after vaccination, no additional HRV vaccine/placebo dose should be administered at this visit.

IMMEDIATE POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time (30 minutes) please fill in the **Solicited Adverse Events** section**,** the **Non-Serious Adverse Event** section or a **Serious Adverse Event** form**.**

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box**.**

13.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 2**		|_____|

CONCOMITANT VACCINE ADMINISTRATION

Infanrix hexa (NA for France)

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year
☐ NA

Infanrix polio Hib (France only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year
☐ NA

Meningitec (Spain only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year
☐ NA

Prevenar (France & Germany only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year
☐ NA

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

14.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 2**		|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

Has the subject experienced any of the following signs/symptoms including diarrhea during the solicited period?

[91] ☐ Information not available
[92] ☐ No vaccine administered
[0] ☐ No
[1] ☐ Yes, please **tick** No/Yes **for each symptom.** If Yes is ticked, please **complete** all items.

GENERAL SYMPTOMS	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Ongoing after day 7?**	**Date of last day of symptoms day month year**	**Causa-lity?**	Medical attention
Fever (FE) ☐ No ☐ Yes → °C : [A] ☐ Axillary [R] ☐ Rectal	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Cough / Runny nose (CO) ☐ No ☐ Yes → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Irritability/ Fussiness (IR) ☐ No ☐ Yes → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Loss of appetite (LO) ☐ No ☐ Yes → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|
Vomiting (VO) ☐ No ☐ Yes → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	HO/ER/MD /AD ☐ No ☐ Yes→ |__|__|

Intensity:
0
1
2
3

Fever: Axillary ≥ 37.5°C
Rectal ≥ 38°C

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

If any of these **adverse events** are **serious** according to Protocol definition, please report event to GSK monitor by telephone or fax within 24 hours (see Protocol) and complete the **Serious Adverse Event form**.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|____|	**DOSE 2**		|_____|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?	Causa-lity?	Medical attention
Diarrhea (DA)(*) ☐ No ☐ Yes (**) → number of looser than normal stools:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→ please fill the GE section	☐ No ☐ Yes	☐ No ☐ Yes→ HO/ER/MD/AD |___|

(*) Stool sample should be collected in case of diarrhea.

Stool collection date : |__|__| |__|__|__| |__|__|__|__| Hour : |__|__| |__|__|
day month year hours min

Stool collection date : |__|__| |__|__|__| |__|__|__|__| Hour : |__|__| |__|__|
day month year hours min

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

(**) If diarrhea yes, please complete the following items.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Irritability/less playfull	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for diarrhea :

☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

16.

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 2**		|_____|

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination ?

[91] ☐ Information not available

[92] ☐ No Vaccine administered

[0] ☐ No

[1] ☐ Yes, fill in the Non-Serious Adverse Event pages or Serious Adverse Event form.

VISIT 3

MONTH 3 or 4

30 – 48 days after Visit 2 for Finland and Italy

49 – 83 days after Visit 2 for Czech Republic, France, Germany and Spain

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa, Infanrix PolioHib, Prevenar and Meningitec in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 3**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 3 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 3**	|__|__| |__|__|__|__| |__|__|__|__|__| day month year	|__|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE (in a subset for Finland)

Has a blood sample been taken ?

☐ Yes → Please complete only if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

☐ No

☐ NA

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from one week after dose 2 until visit 3 ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

CONCOMITANT VACCINE ADMINISTRATION

According to the local national Plan of Immunization, the third dose of routine vaccinations should be done at 4 months age in France and Germany at 5 months age in Czech republic and at 6 months age in Spain.
Please report the vaccine administration date :

Infanrix hexa (France, Germany, Spain and Czech Republic only, NA for the other countries)

☐ No

☐ Yes → please complete the date : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

☐ NA

Prevenar (France & Germany only, NA for the other countries)

☐ No

☐ Yes → please complete the date : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

☐ NA

Meningitec (Spain only, NA for the other countries)

☐ No

☐ Yes → please complete the date : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

☐ NA

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

19.

VISIT 4

MONTH 5

30 – 48 days after the third dose of childhod vaccines

SPAIN ONLY

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa, Infanrix PolioHib, Prevenar and Meningitec in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 4**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 4 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes → Please complete only if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

☐ No

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 3 until visit 4 ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

VISIT 5

mid June to end July 2005

End of the first efficacy follow-up period

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

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.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 5**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 5 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 5**	|___|___| |___|___|___| |___|___|___|___| day month year	|___|___|___|___|___|___|___|

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 3 until visit 5 (from Visit 4 to Visit 5 in Spain)?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

GASTROENTERITIS EPISODES UP TO VISIT 5

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

Has any gastroenteritis occurred from Visit 1 until Visit 5 excluding those recorded on the solicited adverse event pages or has any gastroenteritis occurred during the solicited period and was still ongoing after day 7 ?

☐ No
☐ Yes → Please complete below and next pages if necessary.

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

<u>Medical attention</u>:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

***Date** The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	→ ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

<u>Medical attention</u>:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

> ***One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.***
> ***A second stool sample can be taken if the first one is insufficient.***

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

|__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

Medical attention:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Medical attention:

HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

CONCOMITANT VACCINATION UP TO VISIT 5

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

CONCOMITANT VACCINATION UP TO VISIT 5

Has any vaccine other than the study vaccine(s) and the routine vaccine been administered during the timeframe as specified in the Protocol up to Visit 5 ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** day month year
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IV = Intravenous
NA = Intranasal
OTH = Other
PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

29.

MEDICATION
UP TO VISIT 5

GlaxoSmithKline Biologicals

Medication route. Please use below defined codes.

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

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study vaccine (HRV vaccine or placebo) are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever is later) are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as ‘Prophylactic’.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for adverse events must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment.

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|__|

MEDICATION UP TO VISIT 5

Have any medications/treatments been administered during the timeframe as specified in the protocol up to Visit 5 ?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	**Medical Indication**	**Total daily dose**	**Route**	**Start and end date or tick 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					

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NON-SERIOUS ADVERSE EVENTS UP TO VISIT 5

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 5

(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 between Visit 1 and Visit 5 or has any non-serious adverse events leading to drop-out occurred ?

☐ No
☐ Yes, please complete the following table.

AE No.	1	2
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

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102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 5 (continued)

AE No.	3	4
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

STUDY

CONCLUSION

AT VISIT 5

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|_____|

STUDY CONCLUSION AT VISIT 5

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 1 and Visit 5 ?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 1 and Visit 5 ?

☐ No ☐ Yes → Complete date and tick one reason below.

|__|__| |__|__|__| |__|__|__|__|
day month year

[1] ☐ Medical emergency requiring identification of investigational product for further treatments

[9] ☐ Other, specify: _____

→ Complete **Non-Serious Adverse Event** section or **Serious Adverse Event** form as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 1 and Visit 5 ?

☐ No ☐ Yes → Specify: _____

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GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|_____|

STUDY CONCLUSION AT VISIT 5 (continued)

Was the subject withdrawn from study?

☐ No
☐ Yes

Please tick the **ONE most appropriate** category for withdrawal.

☐ [SAE] Serious adverse event
(check **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event
(check the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [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: _____

Please tick who took decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

34.

VISIT 6

MONTH 9 (Italy)
MONTH 10 (Finland)

30 – 48 days after the third dose of childhod vaccines

ITALY AND IMMUNO SUBSET FOR FINLAND ONLY

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 6**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 6 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 6**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 5 until visit 6 ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**
→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

CONCOMITANT VACCINE ADMINISTRATION

According to the local national Plan of Immunization, the third dose of routine vaccinations should be done at 11months age in Italy and 12 months age in Finland.
Please report the vaccine administration date :

Infanrix hexa

☐ No

☐ Yes → please complete the date : |__|__| |__|__|__| |__|__|__|__|
day month year

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

VISIT 7

mid June to end July 2006

End of the second efficacy follow-up period

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 7**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 7 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 7**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 5 until visit 7 (from Visit 6 until Visit 7 in Finland and Italy) ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

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GASTROENTERITIS EPISODES

VISIT 5 TO 7

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Has any gastroenteritis occurred from Visit 5 until Visit 7 ? ☐ No
☐ Yes → Please complete below and next pages if necessary.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

<u>Medical attention</u>:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	→ ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

<table>
<tr><td>Protocol</td><td>CRF</td><td></td><td></td><td></td><td>Subject Number</td></tr>
<tr><td>102247</td><td>|___|</td><td></td><td></td><td></td><td>|__|__|__|__|__|__|__|</td></tr>
</table>

GASTROENTERITIS EPISODE

Episode n° |__|__|

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Medical attention:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

|__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

<table>
<tr><th>Date <i>The first and last date to be considered is the first and last date with at least 3 looser than normal stools.</i>
day month year</th><th>Number of looser than normal stools per day</th><th>Number of vomiting per day</th><th>Temperature
°C</th><th>→ ☐ Axillary
☐ Rectal</th><th>Irritability / Less playfull</th><th>Lethargic</th><th>Listless</th><th>Seizure</th></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__|.|__|</td><td>☐ not taken</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__|.|__|</td><td>☐ not taken</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__|.|__|</td><td>☐ not taken</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__|.|__|</td><td>☐ not taken</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__|.|__|</td><td>☐ not taken</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td><td>☐ No ☐ Yes</td></tr>
</table>

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| day month year |__|__|:|__|__| hours min

|__|__| |__|__|__| |__|__|__|__| day month year |__|__|:|__|__| hours min

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

42.

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes → |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Medical attention:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	→ ☐ Axillary ☐ Rectal	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

CONCOMITANT VACCINATION VISIT 5 TO 7

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) and the routine vaccine been administered during the timeframe as specified in the Protocol between Visit 5 and Visit 7 ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** day month year
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IV = Intravenous
NA = Intranasal
OTH = Other
PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

44.

MEDICATION
VISIT 5 TO 7

GlaxoSmithKline Biologicals

Medication route. Please use below defined codes.

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

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study vaccine (HRV vaccine or placebo) are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever is later) are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as ‘Prophylactic’.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for adverse events must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment.

102247 (Rota-036)

<table>
<tr><td>Protocol</td><td>CRF</td><td></td><td></td><td>Subject Number</td></tr>
<tr><td>102247</td><td>|___|</td><td></td><td></td><td>|___|___|___|___|___|___|</td></tr>
</table>

MEDICATION

Have any medications/treatments been administered between Visit 5 and Visit 7 ?

☐ No
☐ Yes, please complete the following table.

<table>
<tr><th>Trade / Generic Name</th><th>Medical Indication</th><th>Total daily dose</th><th>Route</th><th colspan="2">Start and end date or tick box if continuing at end of study
day month year</th></tr>
<tr><td></td><td>☐ Prophylactic</td><td></td><td></td><td>Start: |__|__| |__|__|__| |__|__|__|__|
End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
<tr><td>For GSK</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>☐ Prophylactic</td><td></td><td></td><td>Start: |__|__| |__|__|__| |__|__|__|__|
End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
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End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
<tr><td>For GSK</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>☐ Prophylactic</td><td></td><td></td><td>Start: |__|__| |__|__|__| |__|__|__|__|
End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
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End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
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End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
<tr><td>For <i>GSK</i></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td>☐ Prophylactic</td><td></td><td></td><td>Start: |__|__| |__|__|__| |__|__|__|__|
End: |__|__| |__|__|__| |__|__|__|__|</td><td>☐</td></tr>
<tr><td>For GSK</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

NON-SERIOUS ADVERSE EVENTS VISIT 5 TO 7

To be filled only in case of drop-out due to non-serious AE.

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP-OUT

AE No.	1	2
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP OUT (continued)

AE No.	3	4
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

STUDY

CONCLUSION

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|_____|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 5 and Visit 7 ?

☐ No ☐ Yes → Specify total number of SAE's: |___|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 5 and Visit 7 ?

☐ No ☐ Yes → Complete date and tick one reason below.

|___|___| |___|___|___| |___|___|___|___|
day month year

[1] ☐ Medical emergency requiring identification of investigational product for further treatments

[9] ☐ Other, specify: _____

→ Complete **Non-Serious Adverse Event** section or **Serious Adverse Event** form as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 5 and Visit 7 ?

☐ No ☐ Yes → Specify: _____

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

STUDY CONCLUSION (continued)

Was the subject withdrawn from study?

☐ No
☐ Yes

Please tick the **ONE most appropriate** category for withdrawal.

☐ [SAE] Serious adverse event
(check **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event
(check the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [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: _____

Please tick who took decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

49.

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 1	_____

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting,

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

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms (day month year)	Medical attention	HO/ER/MD /AD
Temperature → °C: ☐ Axillary ☐ Rectal	__._	__._	__._	__._	__._	__._	__._	__._	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Cough/runny nose → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Irritability/ Fussiness → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Loss of appetite → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Vomiting → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __ __ ____

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**DOSE 1**	_____

SOLICITED GENERAL SYMPTOMS

II. Diarrhea

DIARRHEA is defined as three or more looser than normal stools within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	
Diarrhea (*) →number of looser than normal stools :	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	If ongoing after day 7, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET

(*) In case of diarrhea (three or more looser than normal stools within a day) please collect a stool sample, assess the occurrence of any of the following symptoms, record whether medical treatment was given and if medical advise has been taken.

DIARRHEA	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Stools samples taken. ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION

- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 1	|__|__|__|__|__|__|__|

FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM

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.

In case of diarrhea starting between day 0 and day 7 and still ongoing on day 7, please continue to assess the following symptoms until the end of the diarrhea.

DIARRHEA	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea → number of looser than normal stools :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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 HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 **(Rota-036)**			**DOSE 1**	

UNSOLICITED SYMPTOMS

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:	**Mild:**	An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2:	**Moderate:**	An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3:	**Severe:**	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).

GENERAL SYMPTOMS OTHER THAN DIARRHEA OR OTHER SOLICITED SYMPTOMS

Description - please give details below	Intensity	Start date day month year	End date or check box if continuing day month year		Medical attention	
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD

Medical attention:

HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

MEDICATION — **Please fill in below if any medication has been taken since the vaccination**

Trade/Generic name	Reason	Route	Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
						☐
						☐
						☐
						☐
						☐
						☐
						☐

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**From day 8 after dose 1 until dose 2**	_____

GASTROENTERITIS EPISODE

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 with or without vomiting.

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, record whether medical treatment was given and if medical advise has been taken.

EPISODE N° : _____

GASTROENTERITIS SYMPTOMS	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
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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:
- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION
- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __/__/____

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 2	_____

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting,

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

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms (day month year)	Medical attention	HO/ER/MD /AD
Temperature → °C: ☐ Axillary ☐ Rectal	__._	__._	__._	__._	__._	__._	__._	__._	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Cough/runny nose → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Irritability/ Fussiness → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Loss of appetite → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__
Vomiting → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	__ __ ____	☐ No ☐ Yes →	__

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __ __ ____

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 2	_____

SOLICITED GENERAL SYMPTOMS

II. Diarrhea

DIARRHEA is defined as three or more looser than normal stools within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	
Diarrhea (*) →number of looser than normal stools :	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	If ongoing after day 7, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET

(*) In case of diarrhea (three or more looser than normal stools within a day) please collect a stool sample, assess the occurrence of any of the following symptoms, record whether medical treatment was given and if medical advise has been taken.

DIARRHEA	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Stools samples taken. ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION

- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**DOSE 2**	|__|__|__|__|__|__|__|

FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM

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.

In case of diarrhea starting between day 0 and day 7 and still ongoing on day 7, please continue to assess the following symptoms until the end of the diarrhea.

DIARRHEA	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea → number of looser than normal stools :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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 HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**DOSE 2**	|_|_|_|_|_|_|

UNSOLICITED SYMPTOMS

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:	**Mild:**	An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2:	**Moderate:**	An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3:	**Severe:**	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).

GENERAL SYMPTOMS OTHER THAN DIARRHEA OR OTHER SOLICITED SYMPTOMS

Description - please give details below	Intensity	Start date day month year	End date or check box if continuing day month year		Medical attention	
						HO/ER/MD/AD
	|_|	|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐	☐ No ☐ Yes →	|_|_|
						HO/ER/MD/AD
	|_|	|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐	☐ No ☐ Yes →	|_|_|
						HO/ER/MD/AD
	|_|	|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐	☐ No ☐ Yes →	|_|_|
						HO/ER/MD/AD
	|_|	|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐	☐ No ☐ Yes →	|_|_|
						HO/ER/MD/AD
	|_|	|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐	☐ No ☐ Yes →	|_|_|
						HO/ER/MD/AD
	|_|	|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐	☐ No ☐ Yes →	|_|_|

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

MEDICATION

Please fill in below if any medication has been taken since the vaccination

Trade/Generic name	Reason	Route	Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐
				|_|_||_|_|_||_|_|_|_|	|_|_||_|_|_||_|_|_|_|	☐

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**From Day 8 after Dose 2 until Study End**	_____

GASTROENTERITIS EPISODE

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 with or without vomiting.

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, record whether medical treatment was given and if medical advise has been taken.

EPISODE N° : _____

GASTROENTERITIS SYMPTOMS	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
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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:
- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION
- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __/__/____

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

List of IEC/IRB

Appendix 2C List of Independent Ethics Committees/Institutional Review Boards

Centre Numbers*	Ethics Review Body	Location
CZECH REPUBLIC		
All centers	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
FINLAND		
All centers	[redacted]	[redacted]
FRANCE		

Centre Numbers*	Ethics Review Body	Location
All centers	[redacted]	[redacted]
GERMANY		
All centers	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany

Centre Numbers*	Ethics Review Body	Location
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
ITALY		
[redacted]	[redacted]	[redacted] (Italy)
[redacted]	[redacted]	[redacted] (Italy)
SPAIN		
All centers	[redacted]	[redacted]

*GSK Biologicals assigned centre number

† [redacted] (Italy) was the original ERC for this center and was replaced by the ERC stated in the table during the course of the study.

Model ICF Amendment 1

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

Confidential & Proprietary Information

Subject Information Sheet and Informed Consent Agreement

GLAXOSMITHKLINE BIOLOGICALS

Subject/Patient Information Sheet and Informed Consent

Study title: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Investigator:

Sponsor: GlaxoSmithKline Biologicals

eTrack study number: 102247

eTrack abbreviated title: rota-036 - Europe

EudraCT number 2004-001175-19

Date of approval: 11 June 2004 – Final Version 1

07 June 2005 –Version 2 (amendment 1)

Prepared by: [redacted] Scientific Writer

CLINICAL RESEARCH AND DEVELOPMENT

GlaxoSmithKline Biologicals

This document should be presented to the subject or patient in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Subject No._____ Date: _____

Introduction

The main objective of this document is to provide the potential study participant with the information necessary to help in deciding to participate in the study with GlaxoSmithKline Biologicals' human rotavirus (HRV) vaccine. The document provides a full but simple understanding of the scientific reasons for investigation of the vaccine, the characteristics, effectiveness and safety of the vaccine, the likely effects and benefits of the study vaccine in the subjects. This document also informs subjects about their rights and responsibilities in participating in the trial.

Rotavirus Disease

The most common cause of diarrheal illness in infants and young children is a virus called "rotavirus". Virtually all children suffer from rotavirus diarrhea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhea with or without vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrheal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Indeed, gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is a leading cause of death in poorer countries.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. GSK Biologicals has developed a new rotavirus vaccine (HRV vaccine) based on a **human rotavirus**. The human rotavirus in the new vaccine has been weakened so that when a child swallows the vaccine, it causes only a mild infection with few or no symptoms. The child is expected to develop antibodies (substance in the blood that fights infection) and thus be protected against rotavirus gastroenteritis.

As of 31 March 2004, over 74,450 infants have been enrolled in clinical trials with GSK Biologicals' HRV vaccine. The HRV vaccine was shown to be safe and well tolerated in adults, children (1-3 years old) and infants (approximately 2 months old). The mild side-effects observed in infants vaccinated with the HRV vaccine were similar to those observed in infants who were given a placebo (a product that looks like the vaccine but has no activity). Also refer to section "Risks associated with the study" on page 9.

GSK Biologicals HRV vaccine was also effective in developing specific antibodies in infants and decreased the occurrence of acute and severe rotavirus gastroenteritis during two years after vaccination in Finland and Latin America (Brazil, Mexico and Venezuela). The HRV vaccine also reduces hospitalization due to rotavirus disease.

Subject No._____ Date: _____

The purpose of the study

This study will be conducted in several countries in the European Union.

The main purpose of this study is to test the efficacy (prevent acute rotavirus gastroenteritis), safety, reactogenicity (side-effects) and immunogenicity (ability to develop antibodies to fight infection) of GSK Biologicals' HRV vaccine in infants when given along with specific childhood vaccinations used in Europe.

A total of 3990 infants will be part of this study (target of 300 infants each in Czech Republic, France, Germany, Italy and Spain and target of 2490 in Finland). Depending on the current practice for routine vaccinations for children, your child/ward will receive the HRV vaccine or placebo twice by mouth, 1 or 2 months apart. Your child's/ward's participation in this study will last until mid-June to end-July 2006.

Some infants will get a placebo (looks like vaccine but has no activity) instead of the HRV vaccine in order to see if any side effects that occur are related to the rotavirus vaccine. Neither you nor your doctor will know whether your child/ward got the HRV vaccine or the placebo until the end of the study (blinded). If needed in case of emergencies, however, the doctor will be given this information.

Approval

This study protocol has been reviewed and accepted by an independent ethics review committee/Institutional review board.

Study Participation

The research staff member will ask you questions to determine if your child/ward can participate in this study.

Once it is determined that your child/ward can participate in the study, you will be asked to read and sign an informed consent. If you give consent for your child/ward to join the study, the doctor will give your child/ward a physical examination. A research staff member will ask you questions about your family composition, your child's/ward's medical history and the medicines that your child/ward may be taking. At each visit, you will also be asked if your child frequents a day care center or not.

Your child/ward will be randomly assigned (like flipping a coin) to one of two groups, with a 2 out of 3 chance of receiving the HRV vaccine and a 1 out of three chance of receiving a placebo. Each child will receive two doses given one or two months apart by mouth. All study subjects will be observed closely for at least 30 minutes following the administration of vaccines.

Subject No._____ Date: _____

Following the national Plan of Immunisation schedule in your country, your child/ward will also receive the following routine childhood vaccinations:

Country	**Vaccinations**	
	Visit 1	**Visit 2**
Czech Republic	Infanrix Hexa®	Infanrix Hexa®
Finland	Infanrix Hexa®	Infanrix Hexa®
France	Infanrix Hexa® and Prevenar®	Infanrix Polio Hib ® and Prevenar®
Germany	Infanrix Hexa® and Prevenar®	Infanrix Hexa® and Prevenar®
Italy	Infanrix Hexa®	Infanrix Hexa®
Spain	Infanrix Hexa® and Meningitec®	Infanrix Hexa® and Meningitec®

Infanrix Hexa®: combination vaccine providing immunization against diphtheria, tetanus, pertussis, Hib, Hepatitis B and poliovirus.
Infanrix Polio Hib®: combination vaccine providing immunization against diphtheria, tetanus, pertussis, Hib and poliovirus
Prevenar®: immunization against Pneumococcal disease.
Meningitec®: immunization against Neisseria meningitidis. Note: Other similar licensed vaccines against MenC may be substituted if Meningitec® is not available.

Thereafter, your child/ward will complete his/her routine childhood vaccination course as per the recommended local national Plan of Immunisation schedule.

The childhood vaccines in this study are licensed for routine infant vaccination course in many countries worldwide and specifically also in the countries where they will be used. Infanrix Hexa® and Prevenar® are licensed in all countries of the European Union, Infanrix Polio Hib® is licensed in France and Meningitec® is licensed in Spain.

All children in this study will have five study visits. If you live in Spain, your child/ward may have an additional study visit at 7 months of age ***if necessary***. If you live in Italy, your child/ward may have an additional study visit at 12 months of age ***if necessary***. If you live in Finland, your child/ward may have an additional study visit at 13 months of age ***if necessary***. The research staff member will notify you if your child/ward will need an additional study visit. (**Amendment 1: 07 June 2005)**

During the study, you should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

Your child/ward will be followed for diarrhea starting from the time of the first vaccine dose until your child completes the study. You will be regularly contacted during the study period to check on your child's/ward's health – if he/she has any diarrhea or any serious illness. During each rotavirus season (from December to end of May), you will be contacted approximately weekly to check if your child/ward had any diarrhea or serious illness. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. Out of the rotavirus season (June to November) you will be contacted approximately every two weeks. In case you are unavailable at the time of contact, at least one more attempt will be made to contact you before the next planned contact.

Subject No._____ Date: _____

If your child/ward develops gastroenteritis (diarrhea with or without vomiting) at any time during the study, you will be asked to complete a "GE" diary card until end of that diarrhea episode. Diarrhea is defined as passage of 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. You will be also asked to provide a stool sample from your child/ward whenever you child/ward develops gastroenteritis and return the samples to the investigator on an ongoing basis. The stool sample should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of gastroenteritis symptoms. Samples collected during the study will be analysed by GSK Biologicals' designated laboratory to detect rotavirus. We will evaluate the number of rotavirus gastroenteritis cases in the group of infants that got the HRV vaccine compared to the group that got placebo to assess the effectiveness of the HRV vaccine. The GE card has short questions on how long and severely sick your child has been, and what medical care you sought, if any.

You may be asked to complete a "Reactogenicity" diary card daily during the first eight days after each HRV vaccine or placebo dose and other vaccines. You will then fill out information on any diarrhea, vomiting, fever, irritability/fussiness, loss of appetite or cough/runny nose during the first eight days after each HRV vaccine or placebo dose. The information collected will allow us to evaluate how your baby feels after vaccination. This information will be collected from 300 children in each country.

You will also receive a "unsolicited AE/medication" diary card to record information on any adverse events that occur between Visit 1 and Visit 3 and to record any medication taken by your child/ward during that time.

Two (in Czech Republic, France and Germany) or three (in Finland, Italy and Spain) blood samples will be taken from 300 children in each country. A blood sample (approximately 1 ml or 1/4 teaspoon) may be taken from your child/ward at Visit 1. A second blood sample (approximately 3 ml or 3/4 teaspoon) may be taken at Visit 3. Children in Spain, Italy and Finland ***will have an additional blood sample (approximately 3 ml or 3/4 teaspoon)*** one month after the third dose of the routine vaccination course. Blood samples collected during the study will be analysed by GSK Biologicals' designated laboratory to detect antibodies to HRV vaccine and other childhood vaccines. (**Amendment 1: 07 June 2005)**

The research staff will review all the study procedures with you in detail. A brief description of the study procedures during each study visit is presented below.

In between these visits you will be asked to provide in all cases of diarrhea a stool sample from your child/ward as early as possible and within 7 days of the diarrhea episode, and complete a GE card.

Subject No._____ Date: _____

Visit 1 (6 to 14 weeks of age):

- You will be asked questions about your child's/ward's health, your child/ward will be examined by the doctor
- You might be asked for a blood sample (1 ml or 1/4 teaspoon) from your child/ward.
- Administration of the first dose of the study vaccines (HRV vaccine or placebo).
- Administration of the first dose of the specific childhood vaccines.
- After vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- You might be asked to complete the "Reactogenicity" diary card.
- You should complete the "unsolicited AE/medication" diary card.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.

Visit 2 (30-48 days after Visit 1 in the Czech Republic, France and Germany / 49-83 days after Visit 1 in Finland, Italy and Spain):

- A physical examination will be carried out.
- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- Administration of the second dose of the study vaccines (HRV vaccine or placebo).
- Administration of the second dose of the specific childhood vaccines.
- After vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.

Subject No._____ Date: _____

- You might be asked to complete the "Reactogenicity" diary card.
- You should complete the "unsolicited AE/medication" diary card.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 3 (30-48 days after Visit 2 in Finland and Italy / 49-83 days after Visit 2 in the Czech Republic, France, Germany and Spain):

- A physical examination will be carried out. ***(Physical examination at this visit can take place in case of request from the nurse or you, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- You might be asked for a blood sample (3 ml or 3/4 teaspoon) from your child/ward.
- During each gastroenteritis episode until the next visit, a “GE” diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 4 (at 7 months of age only for children from Spain):

Visit 4 is optional and may be combined with Visit 5. (**Amendment 1: 07 June 2005)**

- A physical examination will be carried out. ***(Physical examination at this visit can take place in case of request from the nurse or you, and can be limited appropriate with local requirements for routine physical examination for a child at this age***

and appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked for a blood sample (3 ml or 3/4 teaspoon) from your child/ward.
- You will return the completed diary card(s).
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 5 (mid-June to end-July 2005):

- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations (Finland and Italy) administered since the previous visit or contact.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 6 (at 12 months of age only for children from Italy OR at 13 months of age only for children from Finland who have provided blood samples at previous study visits):

Visit 6 is optional and may be combined with Visit 5. (**Amendment 1: 07 June 2005)**

Subject No._____ Date: _____

- A physical examination will be carried out. ***(Physical examination at this visit can take place in case of request from the nurse or you, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked for a blood sample (3 ml or 3/4 teaspoon) from your child/ward.
- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 7 (mid-June to end-July 2006):

- You will return the completed GE diary card.
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.
- Study end.

Risks associated with the study

Your child/ward will receive a combination vaccine (Infanrix Hexa®) to provide routinely recommended childhood vaccinations against six diseases in one injection. In France the second dose of the combination vaccine will be Infanrix Polio Hib®, in accordance with local immunization practices. If recommended by the local national Plan of Immunisation in your country, your child/ward may also receive vaccination against meningitis caused by Neisseria meningitidis C (e.g. Meningitec®) and/or severe bacterial infection caused by Streptococcus pneumoniae (e.g. Prevenar®) along with each HRV

vaccine or placebo dose. These vaccines may cause side effects including pain and swelling at the injection site, high fever or crying.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, may occur, however, immediate medical assistance will be available following vaccination.

The HRV vaccine to be tested in this study has been shown to be safe in earlier studies with adults, children and infants. Few side effects such as mild fever, loose stools or vomiting have been reported. The vaccine will not cause the rotavirus disease.

Up to recently (as of 31 March 2004), serious illness associated with use of the HRV vaccine has been rare. In clinical trials with GSK Biologicals' HRV vaccine with over 74,450 infants enrolled, a total of 28 serious adverse events considered as possibly related to HRV vaccination have been reported. No deaths considered related to use of this HRV vaccine have occurred.

A vaccine based on a monkey (rhesus) strain of rotavirus was produced in the past in the USA by another company and it was noted after over a million doses had been administered that intussusception occurred very rarely as an illness in association with use of that vaccine. This product was subsequently taken off the market. Intussusception (telescoping of the intestine) is a spontaneous but rarely occurring event. As an example, in Finland it occurs in about 1 child in 2500 and there are about 15 cases of intussusception per year in children under 1 year of age.

In our studies (as of 18 May 2004) intussusception has been identified in 39 children in the entire HRV development program in which over 74,450 children have participated. For most of the cases it is not known if the children received HRV vaccine or placebo. An independent monitoring group reviews all cases, blinded (if the study is not finished) and unblinded (when the study is completed), on a regular basis and this board has up to May 2004 confirmed there are no concerns with the HRV vaccine. All intussusception cases were diagnosed promptly and treated immediately. These cases are considered to be coincidental and no conclusion regarding relationship with vaccination can be drawn from these cases at this time. It should be noted that GSK Biologicals' HRV vaccine is based on a **human** rotavirus and is different from RotaShield® vaccine that was based on a live rotavirus from monkeys.

The intussusception is usually quickly recognized and successfully treated. Your doctor and his/her staff will be well aware of the problem of intussusception and will take appropriate actions to evaluate and treat the condition. Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and high fever (even up to 41°C). The majority of intussusception cases resolve either spontaneously or can be treated effectively and completely with air

contrast enemas. Surgical intervention is usually required in only a few cases. If you are interested, your doctor can provide you with more information regarding intussusception.

During the study, you should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs. If your child/ward has an intussusception, stool samples (or rectal swabs), throat swabs and blood samples from your child/ward will be collected to study its cause. If applicable, tissue specimens (such as intestinal resection specimens, lymphnodes, and the appendix) will be taken during the surgery.

You will be informed in a timely manner of any new findings developed during the course of this research study which might influence your decision on your child's/ward's participation to the trial.

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

There is no licensed rotavirus vaccine currently available for widely use.

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.

Joining this study is voluntary. If you decide not to join, there will be no penalty. You and your child/ward will lose no benefits.

Confidentiality and source document review

You understand and consent to the following:

It will be necessary for representatives of GlaxoSmithKline or possibly health authorities / drug regulatory agencies to access your child's/ward's medical records. Your child's/ward's participation in the study will be treated as confidential, that is, any personally identifiable information will be held and processed under secure conditions at GlaxoSmithKline (or an agent of GlaxoSmithKline) with access limited to appropriate GlaxoSmithKline staff or other authorized agents having a requirement to maintain the confidentiality of the information. Your child/ward will not be referred to by name in any report of the study. Your child's/ward's identity will not be disclosed to any person,

Subject No._____ Date: _____

except for the purposes described above and in the event of a medical emergency or if required by law.

Your child's/ward's data will be processed electronically to determine the outcome of this study, and to provide it to health authorities / drug regulatory agencies. Your child's/ward's data may be transferred to other countries (such as India, USA…) for these purposes GlaxoSmithKline 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 or scientific research purposes. If your child's/ward's data is used for any other purpose it will first be de-identified, that is all personally identifiable information will be removed, and will be processed in a de-identifiable form.

You may be entitled under law to access 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 your child/ward from the study at any time and you/he/she will be under no further obligation for any samplings or vaccinations.

Also, your child's participation in the study may be stopped or not initiated for any of the following reasons:

1. If you don't follow the investigator's instructions.
2. The investigator decides it is in the best interest of your child's health and welfare to discontinue.
3. There aren't enough patients in the study, or the study has reached the required number of patients.
4. GlaxoSmithKline Biologicals stops the study at this study site for other reasons not known now.

If you have any questions, please contact:

Name of investigator: _____

Address of investigator: _____

Subject No._____ Date: _____

Telephone number of investigator: _____

Fax number of investigator: _____

Benefits of the study:

Your child/ward may have the benefit of being protected against rotavirus diseases. In addition, your child/ward will be offered a combination vaccination that provides immunization against up to six diseases in a single injection.

Blood samples taken from your child/ward will be used to determine if your child/ward has developed immunity to the study vaccine and the routine vaccines. Such tests are not normally done and are a benefit of participating in this study.

By participating in this study, you will help in the evaluation of this vaccine and ultimately may make it available for babies to protect them from rotavirus diseases.

There will be no charge for study-related doctor visits, examinations, and laboratory tests. All study vaccines will be provided free of charge.

Compensation:

If your child/ward 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 costs of such treatment will be paid for by GlaxoSmithKline Biologicals. All participants in the study are covered by global insurance policy contracted by GlaxoSmithKline 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: _____

Subject No._____ Date: _____

Telephone number of investigator: _____

Fax number of investigator: _____

Subject No._____ Date: _____

Informed Consent

The HRV vaccine study has been clearly explained to me and I have read and understood the information provided. I agree that my [son/daughter/ward**] participates in the study. I understand that I have the right to decline that my son/daughter/ward enters the study and to withdraw her/him from it at any time for any reasons, without consequence to his/her present or future health care and attention which my child/ward 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)

Witness: _____
(if applicable)

Subject No._____ Date: _____

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)

List of Investigators

Appendix 2E List of investigators and other important participants in the study

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof [redacted]	[redacted]	[redacted] FINLAND
CZECH REPUBLIC			
National Coordinating Principal Investigator	Ass. Prof. [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
FINLAND			
National Coordinating Principal Investigator	Prof [redacted]	[redacted]	[redacted] FINLAND
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof		FINLAND

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof [redacted]	[redacted]	[redacted] FINLAND
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
FRANCE			
All centers (coordinating investigator)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof		FINLAND
GERMANY			
		Dr. med.	
		Dr. med.	
		Dr. med.	
		Dr. med.	
		Germany	
	Dr.	Dr. med.	
		Dr. med.	
		Germany	

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof		FINLAND
		Dr. med.	
		Germany	
		Dr. med.	
		Dr. med.	
		Drs.	
		Germany	
		Dr. med.	
		Dr. med.	
		Dr. med.	
		Dr. med.	
		Germany	
		Dr. med.	
		Dr. med.	
		Drs.	
		Dr. med.	
		Drs.	
		Drs.	
		Drs.	
		Dr. med.	
		Dr. med.	
		Dr. med.	
ITALY			

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof [redacted]	[redacted]	[redacted] FINLAND
[redacted]	[redacted]	[redacted]	
SPAIN			
[redacted]	[redacted]	[redacted]	[redacted]

†Prof. [redacted] was designated to oversee the study and approve the study report
GSK Biologicals assigned centre number

Investigator CV

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Investigator Signature

Appendix 2G Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals
Clinical Research and Development

Investigator Approval Page

STUDY TITLE: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Study: 102247 (rota-036) Development Phase: [IIIb]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator: [redacted]

Affiliation: [redacted]

Signature of Investigator: [redacted]

Date: 3 March 2006

Audit Certificate

Appendix 2H Audit certificates

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines.

During the conduct and reporting of this study, the following independent audits were performed by or on behalf of GlaxoSmithKline Clinical Compliance.

Study Number	Audit Type	Country	Audit Date
444563 (Rota)/036	Clinical Investigator	Finland	13 April 2005
444563 (Rota)/036	Clinical Investigator	Finland	14 September 2005
444563 (Rota)/036	Clinical Investigator	Spain	25 October 2005

Interim Audit Certificate to coincide with the first efficacy follow up analysis and preparation of clinical study report. Information on subsequent audits will be contained in a consolidated Audit Certificate prepared following completion of the study.

Clinical Compliance hereby confirm that the audits detailed above were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP and appropriate standard operating procedures and policies.

Name: [redacted] **Date: 14 November 2005**

Role: Director, European Clinical Compliance, GlaxoSmithKline Research and Development

Documentation of statistical methods

Appendix 2l Documentation related to statistical methods

Confidence interval for a proportion within a group

Letθ, the parameter used for indicating the proportion of subjects in a (infinite) target population developing a specified characteristic within a specified follow-up period after an assumed vaccination. Let N be the size of a randomly selected sample from this population. If n is the number of subjects presenting a given characteristic among these N subjects, the true percentage of subjects with the characteristic ('θ') can be estimated by (n/N)*100. Its exact (1-α)% confidence interval is obtained from:

$$\frac{1}{1+\frac{2*(N+1-n)}{2*n*finv(\alpha/2,2*n,\ 2*(N+1-n))}}$$ as the lower boundary

and

$$\frac{1}{1+\frac{2*(N-n)}{(2*n+2)*finv((1-(\alpha/2)),2*n+2,\ 2*(N-n))}}$$ as the upper boundary.

where finv(probability, degrees of freedom 1, degrees of freedom 2) returns the inverse of the F probability distribution and α is the type I error rate.

Confidence interval for a geometric mean within a group

Let m be the parameter used for indicating the median of the titers obtained after an assumed vaccination in a (infinite) target population. Let N be the size of a randomly selected sample from this population. If T_i is the antibody titer measured for a subject i (i=1,...., N), then, assuming a log normal distribution for T_i, the true median is derived from the geometric mean titer as

$$GMT = 10^{\left(\sum_{i=1}^{N}\log_{10}(T_i)\Big/N\right)}$$

and its (1-α)% confidence interval is obtained from

$$LL = 10^{(LL^*)} \text{ with } LL^* = GMT - tinv(1-(\alpha/2), N-1)*\left(SSD/(N*(N-1))\right)^{1/2}$$

$$UL = 10^{(UL^*)} \text{ with } UL^* = GMT + tinv(1-(\alpha/2), N-1)*\left(SSD/(N*(N-1))\right)^{1/2}$$

as lower limit and upper boundary, respectively

where tinv(p, N-1) returns the p^{th} percentile of the Student's t distribution with (N-1) degrees of freedom, α is the type I error rate and SSD is the sum of the squared deviations on the $\log_{10}$ transformed antibody titers.

Confidence interval for a vaccine efficacy

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{rn2}$$

where n1 = number of cases in the vaccine group
N1 = number of subjects in the vaccine group

n2 = number of cases in the placebo group

N2 = number of subjects in the placebo group

N1/N2 = r

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 binomial 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 (refer above for calculation of CI for a proportion within a group).

Publications based on the study

Appendix 2J Publications based on the study

As of March 02, 2006, there are no publications based on this study.

Publications referenced in the report

This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.

CRFs for SAEs

Appendix 2L CRFs for SAEs and withdrawals due to adverse events

This document is provided as 2 separate PDF files

- ROTA-036 (102247) CRFs for SAEs PART 1
- ROTA-036 (102247) CRFs for SAEs PART 2

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 ***GSK Clinical Study Register****.*

GlaxoSmithKline Biologicals
Clinical Research and Development

Sponsor Signatory Approval Page

STUDY TITLE: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Study: 102247 (rota-036) Development Phase: [IIIb]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director

Signature: [redacted]

Date: 2 March 2006

GlaxoSmithKline Biologicals

Study Title

A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccinations.

Annex Clinical Study Report for Study 102247 (Rota-036)

(Development Phase IIIb)

INDICATION STUDIED: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.

Study Initiation Date:	08 September 2004
Study Completion Date:	10 August 2006
Date of report:	March 2007
Report scope:	This annex report complements the Study Report for Study 102247 (Rota-036) dated 03 March 2006 and presents: • the analyses of efficacy data from Dose 1 of HRV vaccine/ placebo up to Visit 7, during the second and combined efficacy periods • Post Dose 2 and 3 immunogenicity of childhood vaccinations in Finland and Italy • Analysis of safety from Visit 1 up to Visit 7.

Sponsor Signatory: [redacted]
Vice President, Clinical R&D New Vaccines and Life Cycle Management.

This study was performed in compliance with Good Clinical Practices including the archiving of essential documents.

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SYNOPSIS OF ANNEX CLINICAL STUDY REPORT FOR STUDY 102247 (ROTA-036)

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

Title of the study: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccinations.

Principal Investigators: This study was conducted by investigators in six European Union countries (Czech Republic, Finland, France, Germany, Italy and Spain). Prof. [redacted] at the [redacted] Finland, was identified as the principal co-ordinating investigator for this study.

Study Centers: Multicenter study. This study was conducted at multiple sites in six European Union countries (Czech Republic, Finland, France, Germany, Italy and Spain).

Publication (reference): Not published for the year 2 study as of March 2007.

Study period: Study Initiation Date: 08 September 2004 Study Completion Date: 10 August 2006.	**Clinical phase:** IIIb

Objectives pertaining to this annex report:

Secondary efficacy objectives for the second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe rotavirus (RV) gastroenteritis (GE) caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Secondary efficacy objectives for the combined efficacy follow-up period:

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.

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

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Secondary immunogenicity objectives:

- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccinations in Finland and Italy.

Secondary safety objectives:

- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of serious adverse events during the entire course of the study.

Study design of the primary study:

Randomized, double-blind, placebo-controlled, multi-country and multi-center study with two parallel groups: Group HRV vaccine and Group Placebo (control group). Subjects in each group were to receive two doses of HRV vaccine or placebo co-administered with the first two doses of the primary childhood vaccination series given according to the national plan of immunization in each country. Infanrix hexa™ was co-administered with each HRV vaccine or placebo dose in each country, except in France where Infanrix Polio Hib™ was co-administered with the 2nd dose of HRV vaccine or placebo. Meningitec® was co-administered in Spain, and Prevenar® was co-administered in France and Germany. The third dose of the primary childhood vaccination series was to be administered according to the national plan of immunization in each country. Data collection was by remote data entry (RDE) using individual electronic case report forms (eCRF).

Number of subjects:	**Total**	**HRV Group**	**Placebo Group**
Enrolled and vaccinated	3994	2646	1348
Completed Visit 7	3883	2566	1317
Analyzed for Safety (Total Vaccinated Cohort)	3994	2646	1348
Analyzed for efficacy: According-to-Protocol (ATP) cohort for efficacy during the combined efficacy period (primary analysis)	3874	2572	1302
ATP cohort for efficacy during the second efficacy period (primary analysis)	3848	2554	1294
Analyzed for immunogenicity: ATP cohort for immunogenicity (primary analysis)	1216	794	422

Diagnosis and criteria for inclusion:

Healthy infants with birth weight > 2000 g who were 6-14 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 at the time of the first visit of the study.

Study vaccine, dose, mode of administration, lot no.:

Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on Study vaccine, dose, mode of administration and lot no.

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

Reference vaccine, dose and mode of administration, lot no.:
Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on reference vaccine, dose, mode of administration and lot no.

Duration of treatment of the study: The study duration from Visit 1 to Visit 7 at the end of the second efficacy period was approximately 20 months.

Criteria for evaluation of efficacy until Visit 7:
For each episode of GE (diarrhea with or without vomiting) occurring during the study, a GE diary card was completed daily until end of GE symptoms. Collection of stool samples during each GE episode for RV detection by Enzyme Linked Immunosorbent Assay (ELISA) (RotaClone ELISA, Meridian Bioscience, USA). All stool samples that were RV positive were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridization assay at Delft Diagnostic Laboratory, the Netherlands to determine the G and the P types. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV. The 20-point Vesikari scale was also used to assess the intensity of each GE episode. Episodes with score ≥11 on the Vesikari scale was defined as severe.

Secondary efficacy endpoints during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Secondary efficacy endpoints during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Criteria for evaluation of immunogenicity of childhood vaccines at post Dose 2 and 3 are presented in this report:
In a subset of subjects in Finland and Italy: Collection of blood samples from subjects in the immunogenicity and reactogenicity subset at post Dose 2 and 3. Serum levels of antibodies to all antigens contained in the co-administered childhood vaccinations were measured using standard assays at post Dose 2 and 3.

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

Secondary immunogenicity endpoints (in a subset of subjects in Finland and Italy):

- Serum levels of antibodies to all antigens contained in each of the different childhood vaccinations at Visit 3 and Visit 6:
  - Serum concentration/titer expressed as GMC/GMTs for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP and anti-HBs serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 International Units (IU)/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-poliovirus type 1 antibody titers ≥ 8
    - anti-poliovirus type 2 antibody titers ≥ 8
    - anti-poliovirus type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 μg/ml
    - anti-HBs antibody concentrations ≥ 10.0 milli International Units (mIU)/ml
  - Seropositivity status:
    - anti-PT antibody concentrations ≥ 5 ELISA Units (EL.U)/ml
    - anti-FHA antibody concentrations ≥ 5 EL.U/ml
    - anti-PRN antibody concentrations ≥ 5 EL.U/ml

Criteria for evaluation of safety from Dose 1 until Visit 7:

In all subjects: Recording of serious adverse events (SAE) during the study period.

Secondary safety endpoint:

- For all subjects, occurrence of SAEs throughout the entire study period.

Statistical methods:

Analyses were performed as per protocol and as described in a reporting and analysis plan, except for the following analyses:

- The percentage of subjects who reported at least one SAEs from Dose 1 of HRV vaccine/placebo were summarized by group, for pooled countries, according to the MedDRA SOC and PTs and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05).
- Vaccine efficacy (VE) on the total vaccinated cohort was calculated for the period from Dose 1 of HRV vaccine or placebo up to Visit 7.

Demography: The age at each vaccination, at Visit 5 and at Visit 7 were summarized by group using descriptive statistics. The gender and race composition were summarized by group.

Analysis of efficacy: The second efficacy period started on the day after Visit 5 and ended at Visit 7. The combined efficacy period started two weeks after Dose 2 of HRV vaccine or placebo and ended at Visit 7. The duration of the second and the combined efficacy follow-up periods was summarized by group. For each efficacy endpoint, the percentages of subjects reporting at least one episode were compared between groups using two-sided Fisher's exact test (significance level of α=0.05). The VE rate for each efficacy endpoint was calculated with its 95% CI. Exploratory VE was also calculated against any RV GE, each isolated RV type, severe RV GE with Clark score >16, by serological status for IgA antibody concentration at Visit 3, by feeding criteria, all cause GE, by country, all cause severe GE hospitalization due to all cause GE and RV GE from Dose 1 up to Visit 7.

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

Analysis of immunogenicity: Seroprotection/seropositivity rates and their exact 95% CI were calculated by group for antibodies measured at post Dose 2 and 3 of routine vaccinations in Finland and Italy. GMCs/GMTs and their 95% CI were calculated by group. The two-sided asymptotic standardized 95% CI for difference (Placebo minus HRV) in post Dose 3 seropositivity/seroprotection rates was calculated for each co-administered antigen for Finland and Italy. The 95% CI for the ratio of post Dose 3 GMCs/GMTs (Placebo over HRV) was computed for each co-administered antigen for Finland and Italy (using a one-way ANOVA model on the logarithm 10 transformation of the titers).

Analysis of safety: The percentage of subjects who reported at least one SAE/IS from Dose 1 of HRV vaccine or placebo up to Visit 7 were computed by group, for pooled countries, and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05). The percentage of subjects who reported at least one SAE from Dose 1 of HRV vaccine or placebo up to Visit 7 were summarized by group, for pooled countries, according to the MedDRA SOC and PTs and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05). Withdrawals until Visit 7 due to AEs or SAEs were described. The P-values were used as an aid to highlight potential imbalances worth further attention (significance level of alpha = 0.05) and care was to be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment, and the rate of false signals could be considerably large due to the number of comparisons. When a potential imbalance between groups was noted, individual SAE cases were reviewed by a sponsor physician and conclusions were based on clinical judgement.

Summary:

Demography Results: For the pooled countries in the ATP cohort during the second efficacy period, the demographic profile of the two groups was similar with respect to median age, height, weight and gender and racial distribution. The median age at Visit 5 or at last contact for year 1 if Visit 5 was not performed was 11 months. The median age at Visit 7 or at last contact for year 2 if Visit 7 was not performed was 22 months. The study population was predominantly White/Caucasian and there were more males than females in both groups.

Efficacy results: Analysis of efficacy was performed on the ATP cohorts for efficacy (primary analysis) and on the total vaccinated cohort (from Dose 1 up to Visit 7).

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

Table 1 presents the VE during the combined efficacy period (Mean duration: 17 months in each group).

Table 1: VE during the combined efficacy period (from two weeks post Dose 2 up to Visit 7)- ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95% CI			95% CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Any RV GE due to circulating wild-type RV									
HRV	2572	85	3.3	2.6	4.1	78.9	72.7	83.8	<0.001
Placebo	1302	204	15.7	13.7	17.8				
Severe* RV GE due to circulating wild-type RV									
HRV	2572	24	0.9	0.6	1.4	90.4	85.1	94.1	<0.001
Placebo	1302	127	9.8	8.2	11.5				
Any RV GE *due to wild-type G1*									
HRV	2572	18	0.7	0.4	1.1	89.8	82.9	94.2	<0.001
Placebo	1302	89	6.8	5.5	8.3				
Severe* RV GE due to wild-type G1									
HRV	2572	4	0.2	0.0	0.4	96.4	90.4	99.1	<0.001
Placebo	1302	57	4.4	3.3	5.6				
Any RV GE due to non-G1 types									
HRV	2572	62	2.4	1.9	3.1	72.9	62.9	80.5	<0.001
Placebo	1302	116	8.9	7.4	10.6				
Severe* RV GE due to non-G1 types									
HRV	2572	17	0.7	0.4	1.1	87.7	78.9	93.2	<0.001
Placebo	1302	70	5.4	4.2	6.7				
Hospitalization due to RV GE									
HRV	2572	2	0.1	0.0	0.3	96.0	83.8	99.5	<0.001
Placebo	1302	25	1.9	1.2	2.8				
RV GE requiring medical attention									
HRV	2572	41	1.6	1.1	2.2	83.8	76.8	88.9	<0.001
Placebo	1302	128	9.8	8.3	11.6				

*episodes with score ≥ 11 points on Vesikari scale

P-value = two-sided Fisher's exact test (significant level of $\alpha = 0.05$)

N = number of subjects included in each group

n (%) = number (percentage) of subjects with at least one specified RV GE episode reported in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

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

Table 2 presents the VE during the second efficacy period.

Table 2: VE during the second efficacy period (Visit 5 up to Visit 7) – ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95% CI			95% CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Any RV GE due to circulating wild-type RV									
HRV	2554	61	2.4	1.8	3.1	71.9	61.2	79.8	<0.001
Placebo	1294	110	8.5	7.0	10.2				
Severe* RV GE due to circulating wild-type RV									
HRV	2554	19	0.7	0.4	1.2	85.6	75.8	91.9	<0.001
Placebo	1294	67	5.2	4.0	6.5				
Any RV GE due to wild-type G1									
HRV	2554	14	0.5	0.3	0.9	83.5	69.3	91.7	<0.001
Placebo	1294	43	3.3	2.4	4.5				
Severe* RV GE due to wild-type G1									
HRV	2554	2	0.1	0.0	0.3	96.5	86.2	99.6	<0.001
Placebo	1294	29	2.2	1.5	3.2	-	-	-	-
Any RV GE due to non-G1 types									
HRV	2554	42	1.6	1.2	2.2	68.2	52.6	78.9	<0.001
Placebo	1294	67	5.2	4.0	6.5				
Severe* RV GE due to non-G1 types									
HRV	2554	14	0.5	0.3	0.9	80.8	63.7	90.4	<0.001
Placebo	1294	37	2.9	2.0	3.9				
Hospitalization due to RV GE									
HRV	2554	2	0.1	0.0	0.3	92.2	65.6	99.1	<0.001
Placebo	1294	13	1.0	0.5	1.7				
RV GE requiring medical attention									
HRV	2554	31	1.2	0.8	1.7	76.2	63.0	85.0	<0.001
Placebo	1294	66	5.1	4.0	6.4				

*episodes with score ≥ 11 points on Vesikari scale

P-value = two-sided Fisher's exact test (significant level of α=0.05)

N = number of subjects included in each group

n (%) = number(percentage) of subjects with at least one specified RV GE episode reported in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

Exploratory endpoints for the combined efficacy period:

VE against any RV GE caused by each isolated non-G1 types:

- VE against any RV GE caused by G2 type was 58.3% [95% CI: 10.1%; 81.0%]
- VE against any RV GE caused by G3 type was 84.8% [95% CI: 41.0%; 97.3%]
- VE against any RV GE caused by G4 type was 83.1% [95% CI: 55.6%; 94.5%]
- VE against any RV GE caused by G9 type was 72.9% [95% CI: 59.3%; 82.2%]

VE against severe RV GE caused by each isolated non-G1 types:

- VE against severe RV GE caused by G2 type was 85.5% [95% CI: 24.0%; 98.5%]
- VE against severe RV GE caused by G3 type was 93.7% [95%CI: 52.8%; 99.9%]
- VE against severe RV GE caused by G4 type was 95.4% [95%CI: 68.3%; 99.9%]
- VE against severe RV GE caused by G9 type was 85.0% [95% CI: 71.7%; 92.6%]

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

The percentage of subjects reporting all cause GE, all cause GE rated as severe or GE requiring hospitalization was significantly lower in the HRV group when compared to the placebo group (P-value <0.001 for each comparison). The VE against all cause GE was 14.2% [95% CI: 5.4%; 22.3%]. VE against all cause GE rated as severe was 49.6% [95% CI: 39.8%; 57.8%]. VE against GE requiring hospitalization was 71.5% [95% CI: 53.4%; 82.9%].

Immunogenicity Results of childhood vaccines in Finland and Italy: The analyses of immunogenicity were performed on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort for the immunogenicity and reactogenicity subset.

Post Dose 3 of childhood vaccines in Finland and Italy:

- For Finland and Italy, a statistically significant difference was not detected between the two groups for post Dose 3 seropositivity/serprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP since the two-sided asymptotic standardized 95% CIs for the treatment differences (placebo minus HRV) contain the value zero.
- For Finland and Italy, a statistically significant difference was not detected between the two groups for post Dose 3 GMCs/GMTs of antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP since the 95% CI for the ratios of GMC/GMT (placebo over HRV) for each antibody contain the value one, except for
  - anti-PT antibody in Finland (higher response for the HRV vaccine group)
  - anti-poliovirus type 2 antibody in Finland (higher response for the HRV vaccine group).
  - anti-PRP antibody in Finland (higher response for the HRV vaccine group)

Safety Results: The analyses of safety were performed on the total vaccinated cohort.

Serious Adverse Events from Dose 1of HRV vaccine/placebo up to Visit 7:

- 11.0% [95%CI: 9.8%; 12.2%] subjects in the HRV group and 13.1% [95%CI: 11.3%; 15.0%] subjects in the placebo group reported at least one SAE (P-value = 0.051).
- Three subjects reported intussusceptions (2 in HRV group and 1 in placebo group). One subject from the HRV group reported intussusceptions, assessed as related to vaccination, on Day 8 post Dose 2 of the HRV vaccine (Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on the SAE narratives).The 2 IS reported efficacy period were assessed as not causally related to vaccination. The observed Risk Difference (HRV minus placebo) for IS reported from Dose 1 of HRV vaccine/placebo up to Visit 7 was 0% [95% CI: -0.35%; 0.21%].
- No fatal events were reported.

When SAEs from Dose 1 of HRV vaccine/placebo up to Visit 7 were classified according to the MedDRA SOCs/PTs, potential imbalance between the HRV group and the placebo group was seen for the following SAEs:

- Potential imbalance in favour of HRV vaccine were noted for SAEs classified under the PTs ‘Gastroenteritis’, ‘Gastroenteritis rotavirus’, ‘Head injury’ and ‘Testicular torsion’. Potential imbalance in favour of HRV vaccine were noted for SAEs classified under the SOC ‘Infections and infestations’. Since the imbalance between the groups was mainly driven by events classified under PTs that are linked or related to "Gastroenteritis disease", the observed difference most likely reflects efficacy of the HRV vaccine in preventing GE related symptoms. The two cases (in the placebo group) reported for each SAE classified under the PTs ‘Head injury’ and ‘Testicular torsion’ is likely a chance finding and not clinically relevant.

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

- Potential imbalance in favour of the placebo was noted for SAE classified under the PT 'Pneumonia'. 28 cases of pneumonia in total were reported from Dose 1 of the HRV vaccine/placebo up to Visit 7 but majority of cases, (19 out of 28 cases) were reported after Visit 5. From the HRV group, only one case was reported within 30 days after vaccination.

Individual cases under MedDRA PT pneumonia were reviewed by sponsor physicians. Clinical review of individual cases by the sponsor physician gave no evidence of clinically relevant findings indicating that the potential imbalance was possibly a chance finding. It should be noted that the potential imbalance between treatment groups based on the specific MedDRA PT pneumonia was not observed for unsolicited AEs reported from Day 0 to Day 30 after any HRV vaccine/placebo doses.

Withdrawals due to adverse events/ serious adverse events:

- Five subjects withdrew due to SAEs (one subject in the HRV group and four subjects in the placebo group)
- Ten subjects withdrew due to non-serious AEs (seven subjects in the HRV group and three subjects in the placebo group).

Conclusions:

- Two doses of GSK Biologicals' HRV vaccine showed consistent and high efficacy over the combined efficacy period from 2 weeks post Dose 2 to Visit 7 at the end of the second RV season.
- Two doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccines were found to be highly effective during the combined efficacy period against:
  - Severe RV GE caused by the circulating wild-type RV. The VE was 90.4% [95% CI: 85.1%; 94.1%].
  - Severe RV GE caused by G1 wild-type. The VE was 96.4% [95% CI: 90.4%; 99.1%].
  - Severe RV GE caused by non G1 types (G2, G3, G4, G9 and G12). The VE was 87.7% [95% CI: 78.9%; 93.2%].
  - Severe RV GE caused by G2 type. The VE was 85.5% [95% CI: 24.0%; 98.5%].
  - Severe RV GE caused by G3 type. The VE was 93.7% [95%CI: 52.8%; 99.9%].
  - Severe RV GE caused by G4 type. The VE was 95.4% [95%CI: 68.3%; 99.9%].
  - Severe RV GE caused by G9 type. The VE was 85.0% [95% CI: 71.7%; 92.6%].
  - Hospitalization due to RV GE caused by circulating wild-type RV. The VE was 96.0% [95% CI: 83.8%; 99.5%].
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention. The VE was 83.8% [95% CI: 76.8%; 88.9%].
  - Any RV GE caused by the circulating wild-type RV. The VE was 78.9% [95% CI: 72.7%; 83.8%].
  - Any RV GE due to G1 wild-type. The VE was 89.8% [95% CI: 82.9%; 94.2%].
  - Any RV GE caused by non G1 types (G2, G3, G4, G9 and G12). The VE was 72.9% [95% CI: 62.9%; 80.5%].

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

- Two doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccines were found to be highly effective during the second efficacy period against:
  - Severe RV GE caused by the circulating wild-type RV. The VE was 85.6% [95% CI: 75.8%; 91.9%].
  - Severe RV GE episodes caused by G1 wild-type. The VE was 96.5% [95% CI: 86.2%; 99.6%].
  - Severe RV GE caused by non-G1 type (G2, G3, G4, G9 and G12). The VE was 80.8% [95% CI: 63.7%; 90.4%].
  - Hospitalization due to RV GE caused by circulating wild-type RV. The VE was 92.2% [95% CI: 65.6%; 99.1%].
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention. The VE was 76.2% [95% CI: 63.0%; 85.0%].
  - Any RV GE caused by the circulating wild-type RV. The VE was 71.9% [95% CI: 61.2%; 79.8%].
  - Any RV GE due to G1 wild-type. The VE was 83.5% [95% CI: 69.3%; 91.7%].
  - Any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12). The VE was 68.2% [95% CI: 52.6%; 78.9%].
- GSK Biologicals' HRV vaccine did not appear to impact on the immunogenicity of any of the antigens contained in the co-administered childhood vaccinations in Finland and Italy.
- There was no evidence for a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 7.

Reference: Ruuska T and Vesikari T, Scand J Infect Dis 1990; 22:259–67.

Date of report: March 2007

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SUPPLEMENTS

The supplements are appended to the Clinical Study Report as a separate document.

Supplements 1- 10 : Analysis of demography

Supplements 11-126 : Analysis of efficacy

Supplements 127-198: Analysis of immunogenicity

Supplements 199-204: Analysis of safety

List of Abbreviations

AE	Adverse event
ATP	According-to-protocol
BCG	Bacille Calmette-Guérin
BMI	Body Mass Index
$CCID_{50}$	median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CI	Confidence interval
DMEM	Dulbecco's Modified Eagle Medium
DTPa	Diphtheria and tetanus toxoids and acellular pertussis
eCRF	Electronic Case Report Form
ED_{50}	50% Effective Dose
ELISA	Enzyme Linked ImmunoSorbent Assay
EL.U	Elisa Units
FHA	Filamentous haemagglutinin
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC/T	Geometric Mean Concentration/Titers
GSK	GlaxoSmithKline
HBs	Hepatitis B surface antigen
HBV	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A

IPV	Inactivated polio vaccine
IRB	Institutional Review Board
IS	Intussusception
IU	International Units
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
mIU	milli International Units
ml	milliliter
PID	Patient identification
PRN	Pertactin
PRP	Polyribosyl ribitol phosphate
PSC	Polysaccharide C
PT	Pertussis toxoid
RCC	Reverse Cumulative Distribution Curve
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SAS®	Statistical Analysis System
SD	Standard Deviation
SMS	Short Message Service
SOC	System Organ Class
SOP	Standard Operating Procedures
U	Units
UL	Upper Limit

VE	Vaccine Efficacy
WRC-GCP	Worldwide Regulatory Compliance-GCP

Commercial vaccines

Infanrix hexa™	GSK Biologicals' combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated polio and *Haemophilus influenzae* type b vaccine
Infanrix Polio Hib™	GSK Biologicals' combined diphtheria and tetanus toxoids, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine
Prevenar®	Wyeth Pharmaceuticals' pneumococcal polysaccharide conjugate vaccine (7-valent)
Meningitec®	Wyeth Pharmaceuticals' meningococcal group C conjugate vaccine

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial were kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. Partially blind is to be used for study designs with different blinding levels between different groups, e.g. double blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study co-ordinator	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring proper conduct of a clinical study.
Combined efficacy follow-up period:	Period starting two weeks after Dose 2 of HRV vaccine or placebo and ended at Visit 7.
Completed:	Subject who completed the final study visit foreseen in the protocol. For this annex report, completed refers to a subject who completed Visit 7.

Diarrhea:	Passage of three or more looser than normal stools within a day.
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.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
First efficacy follow-up period:	Period starting from two weeks after Dose 2 of HRV vaccine or placebo and ending at Visit 5.
Gastroenteritis:	Diarrhea with or without vomiting.
Independent Data Monitoring Committee (IDMC):	The IDMC was responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical attention:	Medical provider contact, advice, visit; emergency room contact or visit or hospitalization.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.

Potential imbalance:	Two sided P-value <0.05 for group difference by two-sided test for the null hypothesis of identical incidence in both groups. (P-values less than 0.05 were used as an aid to highlight potential difference worth further attention. However, care must be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment and clinical significance must be taken into account).
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Rotavirus gastroenteritis:	An episode of gastroenteritis occurring after Dose 1 of study vaccine or placebo 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 onset of the next gastroenteritis episode, if subject had several episodes of gastroenteritis were considered.
Rotavirus season:	The rotavirus epidemic season is expected from beginning of December to the end of May in Europe.
SBIR:	A central randomization system on Internet.
Second efficacy follow-up period:	Period starting on the day after Visit 5 and ending at Visit 7.
Serious adverse event:	Any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect in the offspring of a study subject, an important medical event that may not have been immediately life-threatening or resulted in death or hospitalization but may have jeopardized the subject or may have required medical or surgical intervention to prevent one of the other outcomes listed in the above definition i.e. intussusception.
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 units (U)/milliliter (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) seronegative for rotavirus.
Seronegative:	A subject with antibody concentration below the assay cut-off value.
Seropositive:	A subject with antibody concentration greater than or equal to the assay cut-off value.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with a score ≥ 11 on a 20-point scoring system (Vesikari scoring system).
Site Monitor:	An individual assigned by the sponsor who was responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	Adverse events recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events was actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study Monitor:	An individual assigned by the sponsor who was responsible for assuring proper conduct of a clinical study.
Subject(s):	Term used throughout the protocol to denote the enrolled individual(s), who participated in the clinical study, either as a recipient of the investigational product(s) or as a control.
Symptom sheet:	Specific pages in the individual case report form onto which the investigator transcribed from the diary card and/or other source documentation on solicited adverse event(s) reported by the parents/guardians.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any adverse event reported in addition to those solicited during the clinical study. Also any “solicited” symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.

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

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, its amendment, informed consent and other information that required pre-approval were reviewed and approved by an investigational center IEC or IRB in each participating country.

Appendix 3B contains the study protocol and Appendix 3C the unique pages of the individual case report form used in the study. Details of IECs or IRBs are presented in Appendix 3D.

1.2. Ethical Conduct of the Study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including the Somerset West, 1996 version of the Declaration of Helsinki.

1.3. Subject Information and Consent

Written informed consent was obtained from each subject's parent/ guardian before any study-specific procedures were performed.

Data collection was by remote data entry (RDE) using individual electronic case report forms (eCRF).

Representative copies of the Informed Consent Forms used in this study are provided in Appendix 3E.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

Prof. [redacted] at the [redacted] Finland, was identified as the principal co-ordinating investigator for this study as 72% of participating subjects were enrolled in Finland. As the principal co-ordinating investigator, Prof. [redacted] was designated to oversee this study and approve the annex study report.

This study was conducted by a total of 104 investigators / study co-ordinators in six countries: Czech Republic (13 investigators), Finland (12 investigators), France (31 investigators), Germany (32 investigators), Italy (2 investigators) and Spain (14 investigators).

Information regarding investigators responsible for the study in each participating country can be found in Appendix 3F. A brief *Curriculum Vitae* for each investigator is provided in Appendix 3G.

GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium was the study sponsor and was responsible for administration of the study including clinical trial supply management.

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician monitor the safety aspects of the human rotavirus (HRV) vaccine clinical development. In this monitor capacity, the IDMC periodically reviewed safety data from this study.

3. INTRODUCTION

Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) among young children in both developed and developing countries. A recent review estimates that 611,000 (range 454,000–705,000) RV-related deaths occur in children under 5 years of age annually [Parashar, 2006]. Of these, 80% of the deaths are estimated in low-income countries of South Asia or sub-Saharan Africa. From 2000 to 2004, RV was estimated to cause 39% of hospitalizations for childhood diarrhea [Parashar, 2006].

Epidemiologic studies have shown that the estimated RV disease burden in different European countries is high [Johansen, 1999; Koopmans, 1999; Mrukowicz, 1999] and most of this burden is due to RV-associated hospitalization of young children. In Europe, the estimated RV associated hospitalization rates among children less than 5 years of age vary from 1 in 33 cases of RV infection in Finland, 1 in 54 in Sweden, 1 in 65 in Poland, 1 in 74 in the Netherlands and 1 in 80 in Spain [Gil, 2004].

Vaccination is considered as the most effective tool to control the global burden associated with RV GE.

GSK Biologicals has produced an oral live attenuated HRV vaccine containing the RIX4414 vaccine strain. The HRV vaccine was developed from the 89-12 vaccine candidate which was well-tolerated, immunogenic and effective in the United States of America (USA) [Bernstein DI, 2002; Bernstein, 1999; Bernstein, 1998].

After initial dose-ranging trials [Vesikari, 2004], protective efficacy of two doses of the HRV vaccine was demonstrated against any and severe RV GE, as well as against hospitalization for RV GE in phase II studies in Finland [Vesikari, 2004] and Latin America (Brazil, Mexico and Venezuela) [Salinas, 2005]. Vaccine efficacy was demonstrated against G1P[8] and G9P[8] RV [Vesikari, 2004; Salinas, 2005]. The HRV vaccine was well-tolerated and immunogenic in infants. In a large, multi-country phase III study in Latin America, VE against severe RV GE and against RV associated-hospitalization was 85% ($P < 0.001$), reaching 100% against more severe RV GE [Ruiz Palacios, 2006] during the first year follow-up. The vaccine was highly effective against G1, G3 and G9 types. A protective trend was observed against the heterotypic G2P[4] strain. Hospitalization for diarrhea of any cause was reduced by 42% [95% CI: 29%; 53%, $P < 0.001$] [Ruiz Palacios, 2006]. The safety trial of 63,225 infants (randomization

1:1) showed no increased risk of intussusception in vaccinated infants compared to placebo [Ruiz Palacios, 2006]. Sustained high protection against severe RV GE was observed during the first 2 years of life with VE of 80.5% [95%CI: 71.3%; 87.1%] during the combined period of follow-up.

The co-administration of childhood vaccinations with the HRV vaccine has been studied in several trials [Salinas, 2005; Dennehy, 2005], and no immune interference between HRV vaccine and childhood vaccinations has been observed.

Continuing evaluation of the HRV vaccine, study Rota-036 was designed to evaluate the efficacy, immunogenicity, reactogenicity and safety of two doses of the HRV vaccine in healthy infants when co-administered with specific childhood vaccinations in the European setting. The immunogenicity of childhood vaccinations was also evaluated to explore any effect of co-administration with the HRV vaccine.

The study report for study Rota-036 dated 03 March 2006 presented the final analyses of data available up to Visit 5 (end of the first efficacy follow-up period). During the first efficacy follow-up period, VE was 87.1% [95% CI: 79.6%; 92.1%] against any RV GE and 95.8% [95% CI: 89.6%; 98.7%] against severe RV GE, 100% [95% CI: 81.8%; 100%] against RV hospitalization and 91.8% [95% CI: 84.0%; 96.3%] against RV-related medical attention. The vaccine significantly reduced severe RV GE by circulating G1, G3, G4 and G9 types. A protective trend was observed against the heterotypic G2P[4] type. Efficacy was also shown against hospitalization due to gastroenteritis of any cause with VE of 74.7% [95% CI: 45.5%; 88.9%]. The reactogenicity and safety profile of two doses of HRV vaccine co-administered with childhood vaccinations was similar to that of the placebo. The HRV vaccine was immunogenic and did not appear to impact on immunogenicity of any antigens contained in each of the co-administered childhood vaccinations.

Efficacy and safety follow-up continued beyond Visit 5 until Visit 7 planned at the end of the second efficacy follow-up period. This annex report presents analyses of efficacy data during the second and combined efficacy periods, efficacy from Dose 1 of HRV vaccine/ placebo up to Visit 7, immunogenicity of childhood vaccines in Finland and Italy after completion of the primary vaccination series, and safety data from Dose 1 of the HRV vaccine/ placebo up to Visit 7.

4. STUDY OBJECTIVES

The study objectives considered for analyses presented in this annex study report are listed below. Refer to the study protocol in Appendix 3B for all study objectives.

4.1. Secondary objectives

Secondary efficacy objectives for the second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Secondary efficacy objectives for the combined efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due

to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Secondary immunogenicity objectives

- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccinations in Finland and Italy.

Secondary safety objectives

- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of serious adverse events during the entire course of the study.

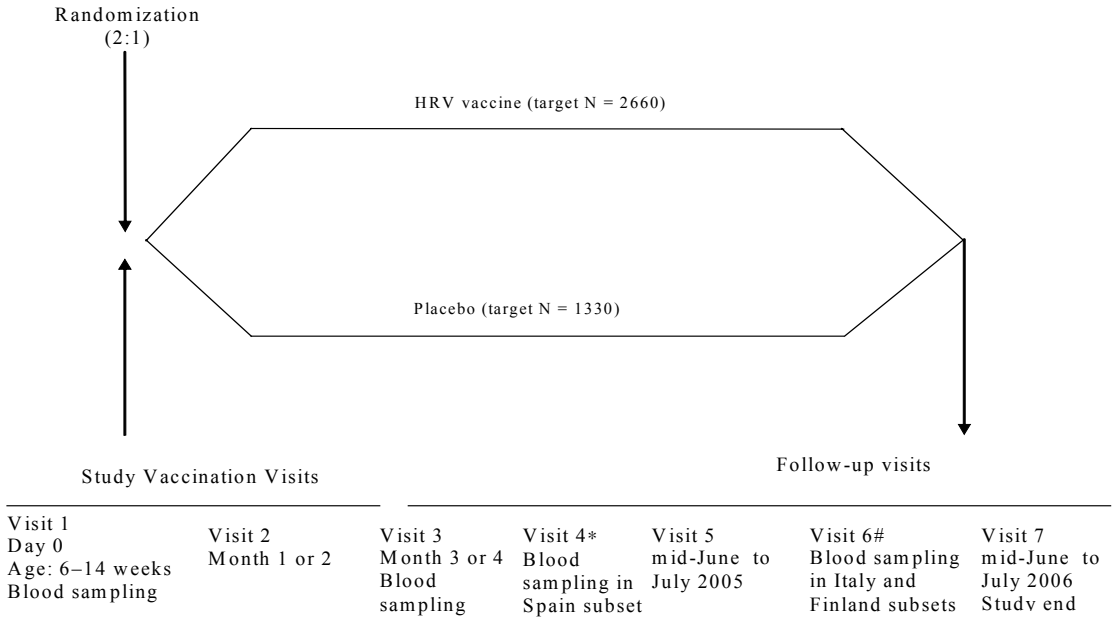
See Section 5.9.1 for secondary endpoints for the objectives listed above.

5. INVESTIGATIONAL PLAN

5.1. Study design

5.1.1. Overall Study Design – Description

Graphic presentation of the study design is presented below with planned enrolment numbers.



Blood sampling only in subjects who were part of the immunogenicity and reactogenicity subset
*At 7 months of age only for subjects in the immunogenicity and reactogenicity subset from Spain (optional).
#At 12 months of age only for subjects in the immunogenicity and reactogenicity subset from Italy (optional). At 13 months of age only for subjects in the immunogenicity and reactogenicity subset from Finland (optional).

This was a randomized, double-blind, placebo-controlled, multi-country and multi-center study conducted in Czech Republic, Finland, France, Germany, Italy and Spain. Eligible subjects were randomly assigned (2:1 randomization ratio) to one of the two parallel groups:

- Group HRV vaccine
- Group Placebo (control group)

Subjects in each group were to receive two doses of HRV vaccine or placebo co-administered with the first two doses of the primary childhood vaccination series given according to the national plan of immunization in each country. The third dose of the primary childhood vaccination series was to be administered according to the national plan of immunization in each country.

The primary vaccination schedules for childhood vaccinations primary series were as follows according to the national plan of immunization in each country:

Czech Republic	3, 4, 5 months of age
Finland	3, 5, 11-12 months of age
France and Germany	2, 3, 4 months of age
Italy	3, 5, 11 months of age
Spain	2, 4, 6 months of age

Data collection was by RDE using individual eCRFs.

The study duration from Visit 1 to Visit 5 at the end of the first efficacy follow-up period was approximately 8 months. The study duration for the second efficacy follow-up period (from the day after Visit 5 up to Visit 7) was approximately 12 months. The total duration of the study (from Visit 1 to Visit 7) was approximately 20 months.

5.2. Study procedures

5.2.1. Outline of study procedures

Table 1 presents the study procedures at visits planned for all subjects in all countries.

Table 1 List of study procedures at visits planned for all subjects in all countries

Age Visit Timing Sampling timepoint	6-14 weeks VISIT 1 Day 0 Pre	VISIT 2 Month 1 or 2	VISIT 3 Month 3 or 4 Post vacc 2	VISIT 5	VISIT 7
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●‡		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in the immunogenicity and reactogenicity subset: for antibody determination	● (1 ml) (planned N=1800)		● (3 ml) (planned N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations*	●	●			
Recording all childhood vaccinations	●	●	●	● Finland and Italy only	
Daily post-vaccination recording of solicited symptoms (Day 0-Day 7) by parents/guardians in a subset (N=1800 planned)	●	●			
Return of reactogenicity diary cards in a subset (N=1800 planned)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800 planned)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination	●	●	●	●	
Recording of unsolicited AEs within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●
Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

Shaded areas refer to study procedures up to Visit 5 which was the end of the first efficacy follow-up period
The double-line border following Month 3 indicates the interim analysis which was performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.
● indicates a study procedure that required documentation in the individual eCRF.
‡ Physical examination was to take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that was to follow (blood draw etc.)
∗ The third dose of the childhood vaccine(s) was to be given according to the respective national Immunization plans of each country. A study visit was not planned specifically for administration of third dose of the childhood vaccine(s).
¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Subjects from Italy and Finland who were part of the "immunogenicity and reactogenicity subset" (planned N=300 per country) had, if necessary, an additional study visit because the blood sampling timepoint one month post Dose 3 of the childhood vaccinations in these countries did not coincide with study visits planned for all subjects.

Table 2 presents the study procedures at optional additional visits planned for subjects in the immunogenicity and reactogenicity subset in Spain, Italy and Finland.

Table 2 List of study procedures at optional additional visits planned for subjects in the immunogenicity and reactogenicity subset in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6)

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2*	VISIT 6 FINLAND only Month 10 Post-vacc 2*	VISIT 6 ITALY only Month 9 Post-vacc 2*
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●‡	●‡	●‡
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in the immunogenicity and reactogenicity subset: for antibody determination (3 ml)	● (planned N=300 from Spain)	● (planned N=300 from Finland)	● (planned N=300 from Italy)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Day 0-Day 7) by parents/guardians in a subset (N=1800 planned)			
Return of reactogenicity diary cards in a subset (N=1800 planned)			
Transcription of the reactogenicity diary card in a subset (N=1800 planned)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination	●	●	●
Recording of unsolicited AEs within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

Shaded areas refer to study procedures before Visit 5 which was the end of the first efficacy follow-up period
● indicates a study procedure that requires documentation in the individual eCRF.
∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of childhood vaccinations.
‡ Physical examination was to take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)
¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Protocol-specified time intervals to be respected between visits are presented in Table 3.

Table 3 Protocol-specified intervals between study visits*

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine vaccination schedule	**3, 4, 5 months**	**3, 5, 11-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccinations
End of the 1st efficacy follow-up period (Visit 5)	Planned in mid-June to end-July 2005				
One month after the third dose of childhood vaccinations	Not applicable	30-48 days after the third dose of childhood vaccinations	Not applicable	30-48 days after the third dose of childhood vaccinations	Not applicable
End of the 2nd efficacy follow-up period (Visit 7)	Planned in mid-June to end-July 2006				

Shaded areas refer to study visits up to Visit 5 which was the end of the first year efficacy follow-up
* = Date of the previous visit/contact was the reference date.

5.2.2. Intervals between Visit 1 and Visit 3 for inclusion in the According-to-Protocol (ATP) immunogenicity cohort

The protocol-specified intervals between Visit 1 and Visit 3 were adapted prior to analysis (See Table 4). These adapted intervals between Visit 1 and Visit 3 served as a criterion for inclusion or exclusion of subjects in the ATP cohort for immunogenicity analysis.

Table 4 Adapted intervals between Visits 1 and Visit 3 for inclusion in the ATP cohort for immunogenicity for subjects in Finland and Italy

Interval	Finland	Italy
Routine vaccination schedule	**3, 5, 11-12 months**	**3, 5, 11 months**
Visit 1-Visit 2	49-83 days	49-83 days
Visit 2-Visit 3	21-48 days	21-48 days

None of the subjects were eliminated from the ATP cohort for immunogenicity for not respecting intervals between other study visits, including the blood sampling visit after Dose 3 of childhood vaccinations.

5.3. Selection of study population

Refer to Study Report for study 102247 (Rota-036) dated 03 March 2006 for inclusion/ exclusion criteria to be satisfied by the subjects at study entry and for contraindication to subsequent dose of study vaccine or concomitantly administered routine vaccines.

5.3.1. Elimination criteria

The following criteria were checked at each visit subsequent to the first visit. If any became applicable during the study, it did not require withdrawal of the subject from the study but it determined a subject's evaluability in the ATP analysis.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids were allowed.)
- Administration of a vaccine 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 immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

5.3.2. Subject completion and withdrawal from study

5.3.2.1. Subject completion

A subject who returns for the concluding visit foreseen in the protocol (Visit 7) is considered to have completed the study.

5.3.2.2. Subject withdrawal from the study

A withdrawal or drop-out was defined as any subject who did not come back for the concluding visit foreseen in the protocol. The investigator(s) attempted to contact those subjects who did not return for scheduled visits or follow-up. Information gathered was specified on the Study Conclusion page of the eCRF. The following possible reasons were responsible for withdrawal of the subject from the study:

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

For this report, drop-outs at the final study visit (Visit 7) were assessed.

5.4. Vaccines composition and administration

Subjects, who were 6-14 weeks of age at the time of the first dose, were to receive two oral doses of HRV vaccine containing $10^{6.5}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 HRV strain or placebo according to 0, 1 or 2-month schedule.

Lot number [redacted] of the HRV vaccine was used. Placebo lot number [redacted] was used. Lot numbers [redacted] and [redacted] were used for the diluent used to resuspend the lyophilized HRV vaccine or placebo.

Commercially available childhood vaccinations (Infanrix hexa™, Infanrix Polio Hib™, Prevenar® and Meningitec®) were co-administered with each HRV vaccine/ placebo dose.

The study vaccine and co-administered childhood vaccinations were to be given according to the national plan of immunization schedule in each country. The vaccination regimen is summarized in Table 5.

Table 5 Dosage and administration

Country	Visit	Vaccination	Dose	Vaccine	Route	Site
Study vaccination						
All	1, 2	RV or placebo	1	HRV or placebo	O	not applicable
Co-administered childhood vaccination						
All, except France	1, 2	DTPa, HBV, IPV, Hib	1	Infanrix hexa™	IM	T
France	1	DTPa, HBV, IPV, Hib	1	Infanrix hexa™	IM	T
	2	DTPa, IPV, Hib	1	Infanrix Polio Hib™	IM	T
France and Germany	1, 2	*Streptococcus pneumoniae*	1	Prevenar®	IM	D/ T
Spain	1, 2	*Neisseria meningitidis* C	1	Meningitec®	IM	D/ T

O = Oral, IM = Intramuscular, D = Deltoid, T = Thigh

The third dose of the primary childhood vaccination series was to be administered according to the national plan of immunization in each country.

5.4.1. Treatment allocation and randomization

At Visit 1, eligible subjects were randomly assigned (2:1 ratio) to the HRV group or the Placebo group. Refer to Study Report for study 102247 (Rota-036) dated 03 March 2006 for details of randomization. Appendix 3H provides the randomization scheme used in this study.

Immunogenicity of childhood vaccines in Finland and Italy after completion of the primary vaccination series was evaluated in the subset of subjects planned to be part of the immunogenicity and reactogenicity subset. For Finland, 300 subjects enrolled at specific centers were to be part of the immunogenicity and reactogenicity subset. All subjects enrolled in Italy were part of the subset. Refer to Study Report for study 102247 (Rota-036) dated 03 March 2006 for details on subsets.

5.4.2. Blinding

The study (treatment administration and follow-up) was conducted in a double-blind manner to allow unbiased evaluation of the HRV vaccine versus the placebo.

No individual codes were held at the local GSK Biologicals' Safety Office or GSK Biologicals' Central Safety Office. The local GSK Biologicals' Safety Office was able to access the individual randomization code from the central randomization system on the Internet. The GSK Biologicals' Central Safety Office accessed the individual randomization code using Matex (a new randomization system at GSK). The code was broken by the Clinical Safety physician (Study Contact for Emergency Code Break in Sponsor Information page) only in the case of medical events that the investigator/ physician in charge of the subject felt could not be treated without knowing the identity of the study vaccine(s). In the event that the code was broken, the reason was recorded in the eCRF and in the subject's medical record.

The IDMC had access to the individual codes and could decode the SAEs to identify the product administered to any subject and evaluate whether enrollment in the study needed to be halted during periodic review of SAEs.

During the analyses performed at the end of the first efficacy follow-up period, access to the individual treatment decode was limited to the statistician and the database administrator to maintain double blinding until study end.

5.4.3. Prior and concomitant medication/vaccinations

After Visit 5 up to Visit 7, at each study visit/ contact, the investigator questioned the subject's parents/ guardian about any medication(s) given to the subject.

Any treatments and/ or medications specifically contraindicated, e.g. any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever was later) were to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

All vaccines administered in the period beginning at birth and ending at the blood sampling visit after completion of the routine three-dose primary vaccination course were to be recorded with trade name, route of administration and date(s) of administration.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for AEs was to be recorded in the eCRF with generic name of the medication (trade names were allowed for combination drugs only), medical indication (including which AE/ SAE), total daily dose, route of administration, start and end dates of treatment.

5.5. Assessment of efficacy variables

Follow-up of GE cases

GE was defined as diarrhea with or without vomiting. Active follow-up for occurrence of GE episodes was conducted starting from administration of Dose 1 of HRV vaccine or placebo until the last visit planned for each subject. The study staff made periodic contact with the subjects' parents/guardians to inquire about the occurrence of GE and any GE related medical care or advice, and hospitalization. This contact was by telephone, short message service (SMS) using cellular phone, an Independent Calling Center or another convenient means. All contacts were to be logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt was to be made before the next planned contact. The frequency of contacts was as follows.

Weekly contact

- From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005

- December 2005 to end of May 2006

Bi-weekly contact

- From June 2005 onwards until 1 December 2005
- June 2006 until study end

Data collection for GE cases

For each suspected GE episode occurring from Visit 1 to study end, a GE diary card was to be completed by the subject's parents/guardians daily until end of the GE episode. The following information was recorded on the GE diary card daily during each suspected GE episode:

- Axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject.
- Rehydration or other medication given to the subjects during the GE episode.
- Medical attention sought for each GE episode (medical personnel contact, advice, visit; emergency room contact or visit or hospitalization).
- Behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or any seizure).

The completed diary cards were to be returned to the investigator at the following study visit. The investigator verified the completed GE diary cards and transcribed the information into the appropriate sections of the eCRF, in English.

Assessment of intensity of GE episodes

The 20-point Vesikari scale

The information from the GE diary card was used to assess the intensity of the GE episodes using the 20-point Vesikari scale [Ruuska , 1990]. Based on the information in the GE diary card, points were assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, use of rehydration therapy or hospitalization for each episode of GE as shown in Table 6.

Table 6 The 20-point Vesikari scale to assess intensity of GE episodes

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode was scored.
§ missing confirmed corresponded to the situation where the route for temperature was omitted in the eCRF and had not been recovered while addressing queries to the investigator

For each episode of GE, a global score (sum of individual points) was calculated. The severity using the 20-points Vesikari scale was defined as below:

- A global score < 7 was prospectively defined as mild,
- A global score between 7 and 10 was prospectively defined as moderate,
- A global score ≥11 was prospectively defined as severe [Ruuska , 1990].

Clark scale for exploratory evaluation

The information from the GE diary card was also used to assess the intensity of the GE episodes using the 24-point Clark scoring system [Clark, 1988] for an exploratory evaluation. In this scale, points were assigned at GSK Biologicals according to duration and intensity of diarrhea, vomiting and fever, as well as on the intensity and duration of behavioral symptoms as shown in Table 7.

Table 7 The 24-point Clark scoring system to assess intensity of GE episodes

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode was scored.
§ Missing confirmed correspond to the situation where the route for temperature was omitted in the eCRF and had not been recovered while addressing queries to the investigator

For each episode of GE, a global score (sum of individual points) was calculated. The severity using the 24-points Clark scale was defined as below:

- A global score < 9 was prospectively defined as mild,
- A global score between 9 and 16 was prospectively defined as moderate,
- A global score > 16 was prospectively defined as severe.

Collection of stool samples during GE

For each suspected GE episode occurring during the study period, a stool sample was to be obtained from the subject. The stool sample was to be collected as soon as possible after symptoms began but not later than 7 days after the onset of GE symptoms. Stool samples collected outside of the 7-day window were also to be submitted for analysis. The stool samples were to be stored preferably at refrigerator temperature (approximately 2-8°C) until they were transferred rapidly to the investigator's laboratory (within 0-3 days). In case a refrigerator was not available, samples could be kept at ambient temperature. The stool samples were stored frozen at approximately -20°C or colder until shipped to GSK Biologicals for analysis.

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 two timepoints either 7 days after the end of the GE episode or the day before onset of the next GE episode if subject had several episodes of GE were used to identify an episode of RV GE.

Analysis of GE stool samples

All GE stool samples were analyzed at GSK Biologicals, Rixensart, Belgium to detect RV antigen using Enzyme Linked Immunosorbent Assay (ELISA) (RotaClone assay from Meridian Bioscience, USA). If a stool sample tested positive for RV, the sample was to be tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridization assay at Delft Diagnostic Laboratory, the Netherlands to determine the G and P types. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV.

5.6. Assessment of immunogenicity variables after Visit 5 up to Visit 7

5.6.1. Laboratory assays and timepoints

Serum analysis at Post Dose 3 of routine vaccinations (Finland and Italy)

Refer to Study Report for Study 102247 (Rota-036) dated 03 March 2006 for details on serum analysis at post Dose 3 of routine vaccinations for all other countries.

Whole blood samples were collected from subjects in the immunogenicity and reactogenicity subset at post Dose 3 of routine vaccinations (Finland and Italy). All blood samples were centrifuged, separated locally and shipped frozen to GSK Biologicals, Rixensart, Belgium. Sera were stored at -20°C until analysis was performed at GSK Biologicals, Rixensart, Belgium using standardized, validated procedures with adequate controls.

Serum levels of antibodies to antigens contained in the co-administered childhood vaccinations were measured using standard assays at post Dose 3 of routine vaccinations.

Table 8 summarizes the laboratory assays performed on serum samples.

Table 8 Serological assays

Antibody	Assay method	Test Kit/ Manufacturer	Assay cut-off	References
Finland and Italy at post Dose 3 of routine vaccinations				
Anti-D	ELISA	in-house	0.1 IU/ml†	[Camargo, 1984]
Anti-T	ELISA	in-house	0.1 IU/ml†	[Melville-Smith, 1983]
Anti-PT	ELISA	in-house	5 EL.U/ml	[Granstorm, 1987; Karpinsky, 1987]
Anti-FHA	ELISA	in-house	5 EL.U/ml	
Anti-PRN	ELISA	in-house	5 EL.U/ml	
Anti-HBs	ELISA	in-house	10 mIU/ml†	
Anti-poliovirus type 1	Micro-neutralization test	in-house	1:8 ED_{50}†	[WHO, 1996]
Anti-poliovirus type 2	Micro-neutralization test	in-house	1:8 ED_{50}†	
Anti-poliovirus type 3	Micro-neutralization test	in-house	1:8 ED_{50}†	
Anti-PRP	ELISA	in-house	0.15 µg/ml†	[Eskola, 1999]

†Seroprotective level
D = Diphtheria toxoid, T = Tetanus toxoid
PT = Pertussis toxoid, FHA = Filamentous haemagglutinin, PRN = Pertactin
HBs = Hepatitis B surface antigen
PRP = Polyribosyl ribitol phosphate
U = Units, IU = International Units
EL.U = Elisa Units, ED_{50} = 50% Effective Dose

Table 9 presents the serology plan.

Table 9 Serology plan for Finland and Italy at post Dose 3 of routine vaccinations

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	Month	Visit no			
Post-vacc 2#	9 (Italy) or 10 (Finland)	6 (Finland and Italy)	D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP	Immunogenicity subset from Finland and Italy	D, T, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, PRP

Post Dose 3 of childhood vaccinations in Finland and Italy.

5.7. Assessment of safety variables

Refer to Study Report for Study 102247 (Rota-036) dated 03 March 2006 for assessment of safety variables from Dose 1 up to Visit 5.

The assessment of safety variables after Visit 5 up to Visit 7 are summarized here.

5.7.1. Adverse events after Visit 5 up to Visit 7

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.

An AE was defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The investigator inquired about the occurrence of AEs/ SAEs at every visit/contact during the study. All AEs either observed by the investigator or one of his clinical collaborators or reported by the subject's parent/ guardian spontaneously or in response to a direct question were evaluated by the investigator. As a consistent method of soliciting AEs, the subject's parent/guardian were 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?" AEs not previously documented in the study were recorded in the Adverse Event form within the subject's eCRF irrespective of severity or whether or not they are considered vaccination-related. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination were established. Details of any corrective treatment were recorded on the appropriate page of the eCRF.

Investigators followed-up subjects

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event had resolved, subsided, stabilized, disappeared, the event was otherwise explained, or the subject was lost to follow-up

AEs already documented in the eCRF, i.e. at a previous assessment, and designated as "not recovered/not resolved" or "recovering/resolving" were reviewed at subsequent visits, as necessary. If these had resolved, the documentation in the eCRF was completed. If an AE changed in frequency or intensity during the specified reporting period, a new record of the event was entered.

When an AE leading to drop out/SAE occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator recorded all relevant information on the eCRF or SAE Report Form as applicable. The investigator attempted to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, ultrasound etc.) that were judged by the investigator to be clinically significant were recorded as AEs or SAEs if they met the definition of an AE, as defined in Section 5.7.1 or SAE, as defined in Section 5.7.2. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were reported as AEs or SAEs. The investigator exercised his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant. Clinically significant

laboratory abnormalities were to be followed up until they had returned to normal, or a satisfactory explanation had been provided.

Assessment of AEs after Visit 5 up to Visit 7

- All AEs leading to subject drop out were recorded on the Adverse Event form in the subject's eCRF.
- All SAEs during the entire study period were recorded in the SAE Report Form. See Section 5.7.2 for definition and reporting of SAEs.

A post-study AE/ SAE was defined as any event that occurred outside of the AE/ SAE detection period defined above. Investigators were not obligated to actively seek AEs or SAEs in former study participants.

Intensity of AEs leading to drop out and SAEs

Based on their clinical judgement, the investigators assessed intensity of the reported AEs leading to drop out and SAEs, as follows:

1 (mild)	=	An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevented normal, everyday activities. (In a young child, such an AE would, for example, prevented attendance at a day-care center and caused the parents/ guardians to seek medical advice)

Relationship between vaccination and AEs leading to drop out and SAEs

The investigators assessed the relationship between investigational product and the occurrence of each event using their clinical judgement.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator therefore assessed whether the AE could be causally related to vaccination rather than to the individual vaccines.

Causality of all AEs was assessed by the investigator using the following question: Was there a reasonable possibility that the AE may have been caused by the investigational product?

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

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

GSK Biologicals could request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE leading to drop-out or SAE. The investigator was obliged to assist.

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined "serious" (see Section 5.7.2 for definition of 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (was to be specified).

Outcome of AE/SAE

Outcome of AE leading to drop out or SAE reported during the study was assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (for SAEs only).

5.7.2. Serious adverse events

A SAE was any untoward medical occurrence that

a. resulted in death,

b. was life-threatening,

c. required hospitalization or prolongation of existing hospitalization,

d. resulted in disability/incapacity,

e. was a congenital anomaly/birth defect in the offspring of a study subject,

f. medical or scientific judgement was exercised in deciding whether reporting was appropriate in other situations, such as important medical events i.e. IS that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

The follow-up of SAEs was performed for all subjects starting from administration of Dose 1 onwards throughout the entire study period (Visit 1 up to Visit 7). SAEs that were related to study participation (e.g. procedures, invasive tests, and a change from existing therapy) or were related to a concurrent medication were to be collected and recorded from the time the subject's parents consented to participate in the study until she/he was discharged.

The investigator inquired about the occurrence of SAEs at every visit/contact during the study. SAEs were to be reported promptly to GSK once the investigator determined that the event met the protocol definition of an SAE. The investigator or designate faxed the SAE reports to GSK Biologicals' Study Contact for reporting SAEs within 24 hours of his/her becoming aware of these events. Additional or follow-up information relating to the initial SAE report was also to be reported to the GSK Biologicals' Study Contact for reporting SAEs within 24 hours of receipt of such information. The investigator provided an assessment of causality, as described in Section 5.7.1, at the time of the initial report. In the event of a death determined by the investigator to be related to vaccination, sending of the fax was to be accompanied by telephone call to the Study Contact for reporting SAEs. If a subject died during participation in the study or during a recognized follow-up period, GSK Biologicals was to be provided with a copy of any available post-mortem findings, including histopathology.

Investigator safety reports were prepared for each SAE according to the current GSK policy and were forwarded to investigators as necessary. An investigator safety report was prepared for a SAE(s) that was both attributable to investigational product and unexpected. The purpose of the report was to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

If an investigator learnt of any SAE, including a death, at any time after a subject had been discharged from the study, and he/she considered the event reasonably related to the investigational product, the investigator was to promptly notify the Study Contact for reporting SAEs.

5.7.2.1. Intussusception

The investigators were required to inform the subject's parents/guardians of the signs and symptoms of IS (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C). Parents/guardians/caretakers of study subjects were instructed to seek medical advice at the nearest hospital in case of symptoms indicative of IS, and to inform the investigator. The investigator and his staff were to take appropriate actions to treat the condition.

The investigators were asked to follow the same procedures for reporting IS cases as for other SAEs. The diagnosis of IS was to be documented by radiography. Documentation by ultrasonography was optional depending on availability of necessary expertise. In addition to the SAE Report Form, an IS Form was also completed for each IS case.

Several biological samples (stool samples (rectal swabs if stool samples not available), throat swabs, blood samples (acute and convalescent sera), and surgical specimens if surgical resection was performed) were to be collected at the treatment site for all IS cases. Tests to be performed on the IS samples were specified in the protocol.

In light of results from the large phase III study Rota-023 (444563/023) that established the safety of GSK Biologicals' HRV vaccine with respect to definite IS [Ruiz Palacios, 2006], the sponsor decided that testing of the IS samples collected during study Rota-036 would be performed only if requested by the Regulatory Authorities. Biological samples collected from IS cases during the present study are being stored at GSK Biologicals, Rixensart, Belgium.

5.8. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, eCRF and safety reporting were reviewed with the investigator and his/her personnel responsible for the conduct of the study by the Company representative(s) 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 and source data/documents. All procedures were performed according to methodologies detailed in GSK Biologicals Standard Operating Procedures (SOPs).

Independent Audit statement:

- During the study period up to Visit 7, this study was subject to audit by GSK's department of Worldwide Regulatory Compliance-GCP (WRC-GCP). Audit certificates are provided in Study Information Appendix 3I.

5.9. Statistical methods for analysis of efficacy, safety and immunogenicity

The statistical methods for analyses of study objectives considered for this annex study report are described.

All statistical analyses were generated by GSK Biologicals, Belgium as planned in the protocol and in a reporting and analysis plan finalized on 03 November 2005 except for changes described in Section 5.10.2. The analyses were performed using SAS 8.2 and Proc StatXact-5 on Windows NT 4.

5.9.1. Secondary endpoints

Secondary efficacy endpoints during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Secondary efficacy endpoints during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Secondary immunogenicity endpoints (in a subset of subjects from Finland and Italy)

- Serum levels of antibodies to all antigens contained in each of the different childhood vaccinations at Visit 3 and Visit 6:
  - Serum concentration/titer expressed as GMC/GMTs for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP and anti-HBs serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 International Units (IU)/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-poliovirus type 1 antibody titers ≥ 8

- anti-poliovirus type 2 antibody titers ≥ 8
- anti-poliovirus type 3 antibody titers ≥ 8
- anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 μg/ml
- anti-HBs antibody concentrations ≥ 10.0 milli International Units (mIU)/ml

– Seropositivity status:

- anti-PT antibody concentrations ≥ 5 ELISA Units (EL.U)/ml
- anti-FHA antibody concentrations ≥ 5 EL.U/ml
- anti-PRN antibody concentrations ≥ 5 EL.U/ml

Secondary safety endpoint:

- For all subjects, occurrence of SAEs throughout the entire study period.

Refer to the study protocol in Appendix 3B for all study endpoints.

5.9.2. Determination of sample size for efficacy evaluation

Refer to Study Report for Study 102247 (Rota-036) dated 03 March 2006 for information on sample size estimation.

5.9.3. Study cohorts/ data sets analyzed

Total vaccinated cohort

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

- a safety analysis based on the total vaccinated cohort included all vaccinated subjects.
- an efficacy analysis based on the total vaccinated cohort included all vaccinated subjects.

Total Vaccinated cohort for the immunogenicity and reactogenicity subset

The total vaccinated cohort for the immunogenicity and reactogenicity subset included all subjects with at least one study vaccine administration documented and for whom solicited symptoms and blood samples were to be collected:

- a reactogenicity analysis based on the total vaccinated cohort for the immunogenicity and reactogenicity subset included all vaccinated subjects for whom solicited symptoms were to be collected.
- an immunogenicity analysis based on the total vaccinated cohort for the immunogenicity and reactogenicity subset included all vaccinated subjects for whom immunogenicity data were available.

ATP cohort for efficacy

The ATP cohort for efficacy included all subjects:

- who received 2 doses of HRV vaccine or placebo according to their random assignment,
- who had entered into the efficacy surveillance period:
  - had follow-up beyond the end of the first efficacy follow-up period for the analysis of the second efficacy follow-up period,
  - had follow-up beyond 2 weeks after Dose 2 of study vaccination for analysis of the combined efficacy follow-up period.
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 was administered and 2 weeks after Dose 2 of HRV vaccine or placebo was administered,
- for whom the randomization code had not been broken,
- who had not received a vaccine forbidden by or not specified in the protocol,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1 of HRV vaccine or placebo for subjects included in the immunogenicity and reactogenicity subset,
- who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind replacement".

ATP cohort for reactogenicity

The ATP cohort for reactogenicity included all vaccinated subjects for whom solicited symptoms were to be collected and

- who had received at least one dose of study vaccine/ control according to their random assignment,
- for whom the randomization code had not been broken,
- who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind replacement",
- who had not received a vaccine forbidden by or not specified in the protocol,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1 of HRV vaccine or placebo.

ATP cohort for immunogenicity

The ATP cohort for immunogenicity included all subjects from the ATP cohort for reactogenicity:

- 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 for HRV vaccine or placebo,
- who complied with blood sampling schedule at Visit 3 (i.e. respected time intervals for blood sampling visits mentioned in Table 4),
- for whom immunogenicity data were available, at pre and post sampling timepoint for anti-rotavirus IgA antibody.
- who had no RV other than vaccine strain in GE stool samples collected up to Visit 3.
- who had no concomitant infection unrelated to the vaccine which might influence the immune response.

Analyzed cohorts

The ATP cohort for efficacy was used for the primary analysis of efficacy. A secondary analysis of efficacy based on the total vaccinated cohort was used to assess VE for the period from Dose 1 up to Visit 7.

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

The total vaccinated cohort was used for the analysis of safety.

5.9.4. Derived and transformed data

Demography

For a given subject and a given demographic variable, missing measurement was not replaced.

Efficacy

An episode of GE was classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain was identified in a stool sample collected during the episode. GE episode without stool sample/ result available was not considered in the analysis as a RV GE episode.

RV GE for efficacy analysis was defined as an episode of GE in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode.

To assess the intensity of RV GE using the 20-point Vesikari scale:

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting) were calculated by counting the number of days with presence (>0) of

looser than normal stool (vomiting). Missing value at a specific day was considered as absence of looser than normal stool (vomiting) at that day.

- The maximum number of looser than normal stool (vomiting or fever) was defined as the maximum value observed from the number of looser than normal stool (vomiting or fever) recorded daily during the GE episode.
- Since the dehydration was not recorded in the eCRF, the following rule was applied: a subject who had a GE episode was considered as being dehydrated between 1 to 5% if this subject received oral rehydration; a subject was considered as being dehydrated > 6 % if the subject was hospitalized and/or received intravenous (IV) rehydration.

To assess the intensity of RV GE using the 24-point Clark scale:

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting, fever or behavioral symptoms) was calculated by counting the number of days with presence (> 0) of looser than normal stool (vomiting, fever or behavioral symptoms). Missing value at a specific day was considered as absence of looser than normal stool (vomiting, fever or behavioral symptoms) at that day.
- The maximum number of looser than normal stool (vomiting or fever) was defined as the maximum value observed from the number of looser than normal stool (vomiting or fever) recorded daily during the GE episode.

Immunogenicity

The cut-off values of all antibodies were defined by the laboratory before the analysis and as described in Section 5.6.1.

A seronegative subject was a subject whose concentration/titer was below the cut-off value.

A seropositive subject was a subject whose concentration/titer was greater than or equal to the cut-off value.

Seroprotection was defined as antibody concentration/titer greater than or equal to the seroprotection level.

The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced.

5.9.5. Analysis of drop-outs, demographics and intercurrent vaccinations

The numbers of subjects who dropped out at Visit 7 were tabulated by group according to the reason for withdrawal.

The median, mean, range and standard deviation of age at Dose 1 and Dose 2 of HRV vaccine or placebo (in weeks), at Visit 5 or at last contact if Visit 5 was not performed (in months) and at Visit 7 or at last contact if Visit 7 was not performed (in months) were calculated by group, for pooled countries and for the ATP cohort for efficacy during the second efficacy period. The racial and gender composition was also presented. The median, mean and standard deviation of height in cm and weight in kg at Visit 1 were also tabulated. The Body Mass Index (BMI) at Visit 1 was also calculated as weight (in kg) / height² (in meters).

The median, mean, range and standard deviation of age at Visit 7 or last contact if Visit 7 was not performed (in months) were calculated by group, by country and for pooled countries, for the total vaccinated cohort.

Epidemiological data in terms of the number of siblings per subject and the attendance to day care center at each visit were tabulated for pooled countries and for each country for the total vaccinated cohort.

The number of days between Dose 2 and Dose 3 of routine childhood vaccinations in Finland and Italy were summarized by group for ATP cohort for immunogenicity and the total vaccinated cohort for the immunogenicity and reactogenicity subset.

The number of days between Dose 3 of routine childhood vaccinations and post-vaccination blood sampling in Finland and Italy were summarized by group for ATP cohort for immunogenicity and the total vaccinated cohort for the immunogenicity and reactogenicity subset.

The number of routine childhood vaccination doses received from Visit 1 up to 21 days before post Dose 3 blood sampling in Finland and Italy were summarized by group for the ATP cohort for immunogenicity and the total vaccinated cohort for the immunogenicity and reactogenicity subset.

5.9.6. Analysis of efficacy

The second efficacy period started on the day after Visit 5 and ended at Visit 7. The combined efficacy period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at Visit 7.

Analysis of efficacy during the second and combined efficacy periods was performed on the ATP cohort for efficacy. Analysis of efficacy from Dose 1 of HRV vaccine or placebo up to Visit 7 was performed on the total vaccinated cohort.

Only GE episodes in which wild-type RV (i.e. other than the vaccine strain) was identified in a stool specimen were included in the efficacy analysis.

A global overview of the number of GE episodes of any etiology (RV or not) and RV GE episodes reported during the second and combined efficacy periods was provided for pooled countries.

Number of GE episodes with no available stool results during the second and combined efficacy periods was provided for pooled countries.

Number of GE episodes and RV GE episodes reported during the second and combined efficacy periods, by severity using the Vesikari scale was presented for pooled countries.

Characteristics of GE episodes reported during the combined efficacy period were tabulated for pooled countries.

A summary of RV GE episodes reported during the second and combined efficacy periods by isolated G and P types was provided for pooled countries and for each country.

Seasonal distributions of the GE episodes and of RV GE episodes reported during the second efficacy period were displayed for pooled countries and for each country.

The duration of the second and combined efficacy periods (in years) was tabulated by group for pooled countries.

For the second and combined efficacy periods, VE estimates were calculated, with their 95% CI against:

- Severe RV GE caused by the circulating wild-type RV
- Severe RV GE caused by G1 type wild-type
- Severe RV GE caused by non-G1 types
- Hospitalization due to RV GE caused by the circulating wild-type RV
- RV GE requiring medical attention caused by the circulating wild-type RV

The VE was defined as the percent reduction in the frequency of the relevant endpoint in vaccinated subjects compared with those subjects who received placebo. This was calculated as follows:

VE = vaccine efficacy = 1- RR = 1 – (ARV/ARU)

Where:

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 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.

RR = relative risk = ARV/ARU

The 95% CIs for VE were derived using a conditional to cases approach. Refer to the Study Report for Study 102247 (Rota-036) dated 03 March 2006 for information on mathematical details about the computation of the 95% CI for VE.

In order to assess VE from Dose 1 onwards, VE against all endpoints evaluated in the ATP analysis was calculated for the period from Dose 1 up to Visit 7. These analyses were performed only on the total vaccinated cohort.

Exploratory VE was also calculated against any RV GE, each isolated RV type, severe RV GE with Clark score >16, by serological status for IgA antibody concentration at Visit 3, by feeding criteria, all cause GE, by country, all cause severe GE and hospitalization due to all cause GE.

For each of the above-mentioned efficacy endpoints, the percentages of subjects reporting at least one episode were compared between groups using two-sided Fisher's exact test (significance level of α=0.05).

5.9.7. Analysis of immunogenicity

Immunogenicity was evaluated in subjects who were part of the immunogenicity and reactogenicity subset.

Immunogenicity of co-administered childhood vaccinations

Post Dose 2 and 3 immunogenicity in Finland and Italy were calculated on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort for immunogenicity and reactogenicity subset.

GMCs/GMTs and seropositivity/seroprotection rates for antibodies to co-administered antigens were calculated with their 95% CIs for each group at post Dose 2 and 3 of childhood vaccinations for Finland and Italy.

Antibody concentrations or titers post Dose 3 of childhood vaccinations were displayed for Finland and Italy using RCCs.

The two-sided asymptotic standardized 95% CI for difference (Placebo minus HRV) in post Dose 3 seropositivity/seroprotection rates was calculated for each co-administered antigen for Finland and Italy.

The 95% CI for the ratio of post Dose 3 GMCs/GMTs (Placebo over HRV) was computed for each co-administered antigen for Finland and Italy (using a one-way ANOVA model on the logarithm10 transformation of the titers).

5.9.8. Analysis of safety

The analyses of safety present numerous group comparisons through P-value computations. The P-values were used as an aid to highlight potential imbalances worth further attention (significance level of alpha = 0.05) and care was to be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment, and the rate of false signals could be considerably large due to the number of comparisons. When a potential imbalance between groups was noted, individual AE

cases were reviewed by a sponsor physician and conclusions were based on clinical judgement.

Safety

Analysis of safety was performed on the total vaccinated cohort.

The verbatim of SAE obtained from the investigators were reviewed by a GSK Biologicals' physician and the signs, symptoms and diagnoses were coded to the most appropriate lowest level term according to according to the MedDRA which was then linked to the primary System Organ Class (SOC) and Preferred Terms (PT) for analysis.

The percentage of subjects who reported at least one SAE/IS from Dose 1 of HRV vaccine or placebo up to Visit 7 were computed by group, for pooled countries, and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05).

The percentage of subjects who reported at least one SAE from Dose 1 of HRV vaccine or placebo up to Visit 7 were summarized by group, for pooled countries, according to the MedDRA SOC and PTs and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05).

The number and percentage of subjects who started taking concomitant medication during the study period were tabulated by type of medication for pooled countries.

Withdrawals until Visit 7 due to AEs or SAEs were described.

5.9.9. Interim analyses

Refer to the Study Report for Study 102247 (Rota-036) dated 03 March 2006 for information on interim analyses performed until Visit 5.

There were no interim analyses during the second efficacy follow-up period.

5.10. Changes in the conduct of the study or planned analyses

5.10.1. Protocol amendments

Refer to the Study Report for study 102247 (Rota-036) dated 03 March 2006 for information on the amendment to the study protocol.

There were no amendments to the protocol during the second efficacy follow-up period.

5.10.2. Other Changes

Analyses were performed as planned in the protocol and in the reporting and analysis plan finalized on 03 November 2005, except for the following changes.

Refer to the Study Report for study 102247 (Rota-036) dated 03 March 2006 for information on additional changes made for the analysis during the first year.

- The percentage of subjects who reported at least one SAE from Dose 1 of HRV vaccine/Placebo were summarized by group, for pooled countries, according to the MedDRA SOC and PTs and compared between groups using two-sided asymptotic standardized 95% CIs for group difference (Risk Difference) and the two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (significance level of alpha = 0.05).
- VE on the total vaccinated cohort was calculated for the period from Dose 1 of HRV vaccine or placebo up to Visit 7.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject was enrolled in this study on 08 September 2004 and the last subject was enrolled on 01 February 2005. The first visit for Visit 5 took place on 24 May 2005 and the last visit for Visit 7 took place on 10 August 2006.

6.2. Subject eligibility and attrition from study

6.2.1. Number and distribution of subjects

Refer to the Study Report for study 102247 (Rota-036) dated 03 March 2006 for details on number and distribution of subjects.

6.2.2. Study completion and withdrawal from study

6.2.2.1. Withdrawal at Visit 7

Table 10 presents the number of subjects vaccinated, completed and dropped-out with reasons for withdrawal.

Of the 3994 subjects who received at least one dose of HRV vaccine or placebo, 3883 subjects completed Visit 7. Reasons for drop-out were as follows:

- Five subjects (one subject in the HRV group and four subjects in the placebo group) dropped-out due to SAEs (Refer to Section 9.3).
- Ten subjects (seven subjects in the HRV group and three subjects in the placebo group) dropped-out due to non-serious AEs. (Refer to Section 9.3)

- 37 subjects (34 subjects in the HRV group and three subjects in the placebo group) dropped-out as the parents/ guardians of these subjects withdrew consent for their child's/ ward's participation. The withdrawal was not due to an AE or SAE.
- 36 subjects (21 subjects in the HR group and 15 subjects in the placebo group) migrated from the study area.
- 23 subjects (17 subjects in the HRV group and six subjects in the placebo group) were lost to follow up. These subjects had completed the vaccination course.

Table 10 Counts of subjects vaccinated, completed and dropped-out with reason for drop-out at Visit 7 – Total vaccinated cohort

	HRV	Placebo	Total
Number of subjects vaccinated	2646	1348	3994
Number of subjects completed	2566	1317	3883
Number of subjects withdrawn	80	31	111
Reasons for withdrawal :			
Serious Adverse Event	1	4	5
Non-serious adverse event	7	3	10
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	34	3	37
Migrated/moved from study area	21	15	36
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	17	6	23
Others	0	0	0

Data source = Appendix table IEi
Vaccinated = number of subjects who where enrolled in the study and received at least one dose of HRV vaccine or placebo
Completed = number of subjects who completed study visit 7
Withdrawn = number of subjects who did not come for study visit 7

6.2.3. Protocol deviations

The protocol deviations according to whether or not they led to exclusion of a subject from an analysis are presented in this section.

6.2.3.1. Protocol deviations leading to exclusion of subjects from an analysis

The number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for efficacy with reasons for exclusion is summarized in Table 11.

Subjects could be attributed more than one elimination code; in the table, subjects are listed on the basis of the lowest elimination code.

ATP cohort for efficacy

The first efficacy period was defined as the period starting from two weeks after Dose 2 of HRV vaccine or placebo and ending at Visit 5.The second efficacy period was defined as the period starting on the day after Visit 5 and ending at Visit 7 and the combined

efficacy period was defined as the period starting two weeks after Dose 2 of HRV vaccine or placebo and ended at Visit 7.

Of the 3994 subjects included in the total vaccinated cohort, 120 subjects (74 subjects in the HRV group and 46 subjects in the placebo group) were eliminated from the ATP cohort for efficacy during the first efficacy period. All subjects included in the ATP cohort for efficacy during the first efficacy period were included in the ATP cohort for efficacy during combined efficacy period. Thus, 3874 subjects (2572 subjects in the HRV group and 1302 subjects in the placebo group) were included in the ATP cohort for efficacy during the first efficacy period and during combined efficacy period.

Of the 3874 subjects included in the ATP cohort for efficacy during the first efficacy period, 26 subjects (18 subjects in the HRV group and eight subjects in the placebo group) were eliminated from the ATP cohort for efficacy during the second efficacy period. These subjects were eliminated as they had not entered into the surveillance period of the second efficacy follow-up period.

Thus, 3848 subjects (2554 subjects in the HRV group and 1294 subjects in the placebo group) were included in the ATP cohort for efficacy during the second efficacy period.

Table 11 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for efficacy with reasons for exclusion – Pooled countries

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total enrolled cohort	**3994**						
Total vaccinated cohort	**3994**		**100**	**2646**		**1348**	
Administration of intercurrent vaccine(s) forbidden in the protocol (code 1040)	10	10		7	7	3	3
Randomisation code broken (code 1060)	1	1		1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	9	9		6	6	3	3
Initially positive or unknown status for serum anti-rotavirus IgA antibodies on the day of dose 1 (code 1500)	52	52		31	31	21	21
At least one study vaccine dose not administered (code 3010)	35	35		25	25	10	10
Subjects not entered into the surveillance period of the first efficacy follow-up period (code 3020)	3	3		2	2	1	1
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response (code 3030)	10	10		2	2	8	8
ATP cohort for efficacy during 1st efficacy period **ATP cohort for efficacy during combined efficacy period**	**3874**		**97.0**	**2572**		**1302**	
Subjects not entered into the surveillance period of the second efficacy follow-up period (code 4020)	26	58		18	40	8	18
ATP cohort for efficacy during 2nd efficacy period	**3848**		**96.3**	**2554**		**1294**	

Data source = Appendix table IA
For cohorts:
n = number of subjects in the cohort.
% = percentage of subjects in the considered cohort relative to the Total vaccinated cohort.
For reasons of exclusion:
Subjects may have more than one elimination code assigned.
Therefore for each elimination code, reason n (s) is provided where:
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number.
s = number of subjects with the elimination code assigned.
The ATP cohort for analysis of efficacy during the first efficacy period and combined efficacy period includes all vaccinated subjects with no elimination codes beginning with one thousand (with the exception of code 1035) or three thousand. The ATP cohort for analysis of efficacy during the second efficacy period includes all vaccinated subjects with no elimination codes beginning with one thousand (with the exception of code 1035) or three thousand or four thousand.

Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on the number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for immunogenicity with reasons for exclusion.

The number of subjects included in the total vaccinated cohort for the reactogenicity and immunogenicity subset (1404 subjects [914 subjects in the HRV group and 490 subjects in the placebo group]) and in the ATP cohort for immunogenicity (1216 subjects [794 subjects in the HRV group and 422 subjects in the placebo group]) is the same as

indicated in the Study report for Study 102247 (Rota-036) dated 03 March 2006. None of the subjects were further eliminated from these cohorts.

6.2.3.2. Protocol deviations not leading to exclusion of subjects from an analysis

Subjects, who completed Visit 7 outside the planned time period of mid-June to end-July 2006, were not eliminated from ATP cohort for efficacy for this reason.

6.3. Demographic characteristics

6.3.1. ATP cohort for efficacy

Demographic characteristics of the ATP cohort for efficacy during the second efficacy period are summarized in Table 12.

For the pooled countries in the ATP cohort during the second efficacy period, the demographic profile of the two groups was similar with respect to median age, height, weight and gender and racial distribution. The median age at Visit 5 or at last contact for year 1 if Visit 5 was not performed was 11 months. The median age at Visit 7 or at last contact for year 2 if Visit 7 was not performed was 22 months. The study population was predominantly White/Caucasian and there were more males than females in both groups.

Table 12 Summary of demographic characteristics – Pooled countries – ATP cohort for efficacy during 2nd efficacy period

		HRV N = 2554		Placebo N = 1294		Total N = 3848	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at dose 1 (weeks)	Mean	11.5	-	11.5	-	11.5	-
	SD	1.77	-	1.78	-	1.77	-
	Minimum	5	-	6	-	5	-
	Median	12.0	-	12.0	-	12.0	-
	Maximum	18	-	15	-	18	-
Age at dose 2 (weeks)	Mean	19.7	-	19.7	-	19.7	-
	SD	2.67	-	2.72	-	2.69	-
	Minimum	10	-	10	-	10	-
	Median	20.0	-	20.0	-	20.0	-
	Maximum	30	-	27	-	30	-
Age at visit 5 or at last contact for year 1 if visit 5 not performed (Months)	Mean	10.3	-	10.4	-	10.3	-
	SD	1.43	-	1.43	-	1.43	-
	Minimum	5	-	5	-	5	-
	Median	11.0	-	11.0	-	11.0	-
	Maximum	13	-	13	-	13	-
Age at visit 7 or at last contact for year 2 if visit 7 not performed (Months)	Mean	22.0	-	22.1	-	22.0	-
	SD	1.49	-	1.57	-	1.51	-
	Minimum	9	-	12	-	9	-
	Median	22.0	-	22.0	-	22.0	-
	Maximum	25	-	27	-	27	-
Gender	Female	1186	46.4	634	49.0	1820	47.3
	Male	1368	53.6	660	51.0	2028	52.7
Race	African heritage	6	0.2	5	0.4	11	0.3
	White/caucasian	2515	98.5	1270	98.1	3785	98.4
	Arabic/north african	9	0.4	3	0.2	12	0.3
	East/south east asian	1	0.0	1	0.1	2	0.1
	South asian	3	0.1	1	0.1	4	0.1
	American hispanic	11	0.4	5	0.4	16	0.4
	Japanese	0	0.0	0	0.0	0	0.0
	Other	9	0.4	9	0.7	18	0.5
Height (cm)	Mean	60.5	-	60.5	-	60.5	-
	SD	2.91	-	2.92	-	2.91	-
	Median	61.0	-	61.0	-	61.0	-
	Unknown	2	-	3	-	5	-
Weight (kg)	Mean	6.0	-	6.0	-	6.0	-
	SD	0.86	-	0.84	-	0.85	-
	Median	6.0	-	6.0	-	6.0	-
	Unknown	0	-	1	-	1	-
BMI (kg/m²)	Mean	16.4	-	16.3	-	16.4	-
	SD	1.51	-	1.54	-	1.52	-
	Median	16.3	-	16.3	-	16.3	-
	Unknown	2	-	3	-	5	-

N = number of subjects in the considered group or in total (sum of both groups)
n (%) = number (percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Data source = Appendix table IB

6.3.2. Total vaccinated cohort

Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on the demography of all subjects in the total vaccinated cohort.

Supplement 1 presents the age (in months) at Visit 7 or last contact, by country and for pooled countries. The median age at Visit 7 or at last contact if Visit 7 was not performed was 22 months.

Supplement 2 presents the summary of data on day care attendance and number of siblings, by country and for pooled countries. For pooled countries, 94.2% of the subjects did not attend a day care center at the time of Visit 5. At Visit 7, only 61.7% of the subjects were still not going to a day care center while 35.5% of the subjects were going to a day care center. Both groups have similar distribution of subjects going to a day care center.

6.4. Concomitant and intercurrent vaccinations

ATP cohort for immunonogenicity

Supplement 3 presents the number of days between the second and third dose of routine childhood vaccination in Finland and Italy. Supplement 4 presents the number of days between the third dose of routine childhood and the post-vaccination blood sample at Visit 5/6 in Finland and Italy. The intervals between the different time points were similar for both groups in Finland and Italy.

The total number of doses of Infanrix hexa™ received from Visit 1 up to 21 days before post Dose 3 blood sampling for Finland and Italy is presented in Supplement 5 and Supplement 6, respectively. A minimum interval of 21 days between Dose 3 and post-vaccination blood sampling was needed to elicit adequate immune response (Refer Table 4).

100% of the subjects in Finland and Italy had received all three doses of Infanrix hexa™ during Visit 1 up to 21 days before post Dose 3 blood sampling.

Total vaccinated cohort for the immunogenicity and reactogenicity subset

Supplement 7 presents the number of days between the second and third dose of routine childhood vaccination in Finland and Italy. Supplement 8 presents the number of days between the third dose of routine childhood and the post-vaccination blood sample at Visit 5/6 in Finland and Italy. The intervals between the different time points were similar for both groups in Finland and Italy.

The total number of doses of Infanrix hexa™ received from Visit 1 up to 21 days before post Dose 3 blood sampling for Finland and Italy is presented in Supplement 9 and Supplement 10, respectively. A minimum interval of 21 days between Dose 3 and post-vaccination blood sampling was needed to elicit adequate immune response (Refer Table 4).

100% of the subjects in Finland and Italy had received all three doses of Infanrix hexa™ during Visit 1 up to 21 days before post Dose 3 blood sampling.

7. VACCINE EFFICACY RESULTS

7.1. Data sets analyzed

The analyses of efficacy were performed on the ATP cohort for efficacy (primary analysis) (combined efficacy period and second efficacy period) and on the total vaccinated cohort (from Dose 1 up to Visit 7). See Section 5.9.3 for the definition of the cohorts identified for analyses and Section 6.2.3.1 for eligibility for analyses.

Only GE episodes in which wild-type RV (i.e. other than the vaccine strain) was identified in a stool specimen were to be included in the efficacy analysis.

7.2. ATP cohort for efficacy during the combined efficacy period

The ATP cohort for efficacy during the combined efficacy period consisted of 3874 subjects (2572 subjects in the HRV group and 1302 subjects in the placebo group).

7.2.1. Characterization of GE episodes

Table 13 presents the percentage of subjects who reported GE episodes of any aetiology (RV or not) and RV GE episodes during the combined efficacy period. Table 14 presents a summary of the intensity of GE episodes and RV GE episodes reported during the combined efficacy period.

Supplement 11 presents the duration (in years) of the follow-up period during the combined efficacy period. Supplement 12 presents the percentage of GE episodes with no available stool results reported during the combined efficacy period.

- During the combined efficacy period (mean duration: 17 months in each group, Supplement 11), 2550 GE episodes of any cause were reported by 1743 subjects. Of these, 1569 GE episodes were reported in 1096 subjects in the HRV group and 981 GE episodes were reported in 647 subjects from the placebo group.
- Stool analysis results were available for 1408/1569 (89.7%) GE episodes in the HRV group and for 863/981 (88.0%) GE episodes in the placebo group. No stool analysis results were available for 161 GE episodes from the HRV group and 118 GE episodes from the placebo group due to insufficient quantity of stool samples collected, stool sample not tested or stools not collected (Supplement 12).
- Of all the GE episodes tested, RV was detected in 85 GE episodes from the HRV group and in 204 GE episodes from the placebo group. No subject in either group had more than one episode of RV GE during the combined efficacy period (Table 13).

- When the RV GE episodes were scored using the 20-point Vesikari scale, 28.2% of the RV GE episodes in the HRV group and 62.3% in the placebo group were rated as severe (Vesikari score ≥ 11 points) (Table 14).

Supplement 13 presents the distribution of Vesikari score for the RV GE episodes.

Table 13 Percentage of subjects who reported GE episodes and RV GE episodes from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Event	Total number of episode reported	HRV N = 2572 n	HRV N = 2572 %	Placebo N = 1302 n	Placebo N = 1302 %
GE	1	754	29.3	404	31.0
	2	239	9.3	179	13.7
	3	80	3.1	46	3.5
	4	20	0.8	10	0.8
	5	1	0.0	7	0.5
	6	2	0.1	1	0.1
	Any	1096	42.6	647	49.7
RV GE	1	85	3.3	204	15.7
	Any	85	3.3	204	15.7

Source: Appendix Table IVB and VA
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 episode

Table 14 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by severity using the 20-point Vesikari scale - ATP cohort for efficacy

Event	Severity using Vesikari scale	HRV n	HRV %	Placebo n	Placebo %
GE	Mild (1-6)	733	46.7	366	37.3
	Moderate (7-10)	548	34.9	319	32.5
	Severe (≥11)	279	17.8	291	29.7
	Unknown	9	0.6	5	0.5
	Any	1569	100	981	100
RV GE	Mild (1-6)	20	23.5	24	11.8
	Moderate (7-10)	41	48.2	53	26.0
	Severe (≥11)	24	28.2	127	62.3
	Any	85	100	204	100

Source: Appendix Table IVB and VA
n (%) = number (percentage) of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported
Any = any specified symptom reported, regardless of Vesikari severity scale

Table 15 presents the number of RV GE episodes by G and P types.

- The G types isolated during the combined efficacy period were G1 wild-type, G2, G3, G4, G9 and G12 types. Genotype P[8] wild-type was associated with G1 wild-type, G3, G4, G9 and G12 types and genotype P4 was associated with G1 wild-type, G2 and G9 types (Table 15).

- The P genotype was not typable for two episodes in the placebo group in which G1 wild-type was isolated from one episode while G2 was isolated from the other episode. The G genotype was not typable for two episodes in the HRV group in which P4 was isolated from the 2 episodes. The RV isolated from five episodes (three episodes in the HRV group and two episodes in the placebo group) were not typable for G and P types (Table 15).
- From the rates in the placebo group, G1P[8] wild-type was the most prevalent type circulating during the combined efficacy period, followed by G9P[8] type. (Table 15).

Table 15 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G serotype and P genotype - ATP cohort for efficacy

	HRV N' = 85		Placebo N' = 204	
Serotype	**n**	**%**	**n**	**%**
G1WT+G4+P8WT	0	0.0	1	0.5
G1WT+G9+P8WT	0	0.0	1	0.5
G1WT and unknown P type*	0	0.0	1	0.5
G1WT+G2+P4	0	0.0	1	0.5
G1WT+P8WT	18	21.2	85	41.7
G2 and unknown P type*	0	0.0	1	0.5
G2+G9+P4	0	0.0	1	0.5
G2+P4	14	16.5	14	6.9
G3+P8WT	3	3.5	10	4.9
G4+P8WT	6	7.1	17	8.3
G9+P8WT	38	44.7	69	33.8
GX+P8WT	1	1.2	1	0.5
P4 and unknown G type*	2	2.4	0	0.0
Unknown G and P type*	3	3.5	2	1.0

Source: Appendix Table IVB and VA
N'= number of RV GE episodes reported
n (%)= number(percentage) of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type
GX = G12
* = not typable

Supplement 14 presents the characteristics of all cause GE episodes during the combined efficacy period. Supplement 15 presents the percentage of subjects with RV GE episodes reported during the combined efficacy period, by G serotype and P genotype. Supplement 16 to Supplement 21 present the characteristics of RV GE for all serotypes and by each serotype reported during the combined efficacy period.

7.2.2. Vaccine efficacy against severe RV GE

Table 16 presents the efficacy of the HRV vaccine against severe RV GE (Vesikari score ≥ 11 points) caused by the circulating wild-type RV during the combined efficacy period.

- The percentage of subjects who reported severe RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the

placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE was 90.4% [95% CI: 85.1%; 94.1%] (Table 16).

Table 16 Percentage of subjects reporting severe (Vesikari score ≥11 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	24	0.9	0.6	1.4	90.4	85.1	94.1	<0.001
Placebo	1302	127	9.8	8.2	11.5				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 22 and Supplement 23 present the efficacy of the HRV vaccine against RV GE with a score ≥ a specific value on the Vesikari scale during the combined efficacy period. The point estimates of VE appear to increase with higher Vesikari score, and reached 100% against RV GE with a score ≥ 17 points on the Vesikari scale.

7.2.3. Vaccine efficacy against severe RV GE by circulating RV types

Table 17 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11 points) RV GE, by isolated RV types during the combined efficacy period. If more than one wild-type RV was detected in specimens from a RV GE episode, then this episode was counted in each of the detected RV type category (Table 17).

- The percentage of subjects who reported severe RV GE episodes caused by G1 wild-type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by G1 wild-type was 96.4% [95% CI: 90.4%; 99.1%] (Table 17).
- The percentage of subjects who reported severe RV GE episodes caused by non G1 types (G2, G3, G4, G9 and G12) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by non G1 types was 87.7% [95% CI: 78.9%; 93.2%] (Table 17).

Type specific VE was observed against severe RV GE (Vesikari score ≥11 points) caused by each of the isolated non G1 types.

- The percentage of subjects who reported severe RV GE episodes caused by G2 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value = 0.009). The VE against severe RV GE caused by G2 type was 85.5% [95% CI: 24.0%; 98.5%] (Table 17).

- The percentage of subjects who reported severe RV GE episodes caused by G3 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value = 0.001). The VE against severe RV GE caused by G3 type was 93.7% [95%CI: 52.8%; 99.9%] (Table 17).
- The percentage of subjects who reported severe RV GE episodes caused by G4 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by G4 type was 95.4% [95%CI: 68.3%; 99.9%] (Table 17).
- The percentage of subjects who reported severe RV GE episodes caused by G9 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by G9 type was 85.0% [95% CI: 71.7%; 92.6%] (Table 17).

Table 17 Percentage of subjects reporting severe (Vesikari score ≥11 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2572	4	0.2	0.0	0.4	96.4	90.4	99.1	<0.001
Placebo	1302	57	4.4	3.3	5.6				
G2									
HRV	2572	2	0.1	0.0	0.3	85.5	24.0	98.5	0.009
Placebo	1302	7	0.5	0.2	1.1				
G3									
HRV	2572	1	0.0	0.0	0.2	93.7	52.8	99.9	0.001
Placebo	1302	8	0.6	0.3	1.2				
G4									
HRV	2572	1	0.0	0.0	0.2	95.4	68.3	99.9	<0.001
Placebo	1302	11	0.8	0.4	1.5				
G9									
HRV	2572	13	0.5	0.3	0.9	85.0	71.7	92.6	<0.001
Placebo	1302	44	3.4	2.5	4.5				
Pooled Non G1 (G2, G3, G4, G9, GX)									
HRV	2572	17	0.7	0.4	1.1	87.7	78.9	93.2	<0.001
Placebo	1302	70	5.4	4.2	6.7				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one specified severe RV GE episode in each group

GX = G12

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

7.2.4. Vaccine efficacy against hospitalization due to RV GE

Table 18 presents the efficacy of the HRV vaccine against hospitalization due to RV GE episodes caused by circulating wild-type RV during the combined efficacy period.

- Two subjects (0.1%) in the HRV group and 25 subjects (1.9%) in the placebo group were hospitalized for RV GE caused by circulating wild-type RV during the combined efficacy period. A significant reduction in hospitalization for RV GE was observed in the HRV vaccine group compared to the placebo group (two sided Fisher's exact P-value <0.001) resulting in VE of 96.0% [95% CI: 83.8%; 99.5%] (Table 18).

Table 18 Percentage of subjects hospitalized due to RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	2	0.1	0.0	0.3	96.0	83.8	99.5	<0.001
Placebo	1302	25	1.9	1.2	2.8				

Source: Appendix Table IVB and VA
N = number of subjects included in each group
n (%) = number(percentage) of subjects hospitalized due to RV GE episode caused by the circulating wild-type RV
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

7.2.5. Vaccine efficacy against RV requiring medical attention

Table 19 presents the efficacy of the HRV vaccine against any RV GE episodes caused by the circulating wild-type RV requiring medical attention (defined in the protocol as medical provider contact, advice, visit; emergency room contact or visit or hospitalization) during the combined efficacy period.

- The percentage of subjects reporting RV GE requiring medical attention was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against RV GE requiring medical attention was 83.8% [95% CI: 76.8%; 88.9%] (Table 19).

Table 19 Percentage of subjects reporting RV GE requiring medical attention and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	41	1.6	1.1	2.2	83.8	76.8	88.9	<0.001
Placebo	1302	128	9.8	8.3	11.6				

Source: Appendix Table IVB and VA
N = number of subjects included in each group
n (%) = number(percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV requiring medical attention in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value=two-sided Fisher's exact test (significant level of α=0.05)

7.2.6. Vaccine efficacy against any RV GE

Table 20 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild-type RV during the combined efficacy period.

- The percentage of subjects who reported any RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE was 78.9% [95% CI: 72.7%; 83.8%] (Table 20).

Table 20 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	85	3.3	2.6	4.1	78.9	72.7	83.8	<0.001
Placebo	1302	204	15.7	13.7	17.8				

Source: Appendix Table IVB and VA
N = number of subjects included in each group
n (%) = number(percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

7.2.6.1. Vaccine efficacy against any RV GE by circulating RV types

Table 21 presents the efficacy of the HRV vaccine against any RV GE, by isolated RV types during the combined efficacy period. If more than one wild-type RV was detected in specimens from a RV GE episode, then this episode was counted in each of the detected RV type category (Table 21).

- The percentage of subjects who reported any RV GE episodes by G1 wild-type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by G1 wild-type was 89.8% [95% CI: 82.9%; 94.2%] (Table 21).
- The percentage of subjects who reported any RV GE episodes caused by non G1 types (G2, G3, G4, G9 and G12) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by non G1 types was 72.9% [95% CI: 62.9%; 80.5%] (Table 21).

Type specific VE was observed against any RV GE caused by each of the isolated non G1 types.

- The percentage of subjects who reported any RV GE episodes caused by G2 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value = 0.020). The VE against any RV GE caused by G2 type was 58.3% [95% CI: 10.1%; 81.0%] (Table 21).
- The percentage of subjects who reported any RV GE episodes caused by G3 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value = 0.002). The VE against any RV GE caused by G3 type was 84.8% [95% CI: 41.0%; 97.3%] (Table 21).
- The percentage of subjects who reported any RV GE episodes caused by G4 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by G4 type was 83.1% [95% CI: 55.6%; 94.5%] (Table 21).

- The percentage of subjects who reported any RV GE episodes caused by G9 type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by G9 type was 72.9% [95% CI: 59.3%; 82.2%] (Table 21).

Table 21 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2572	18	0.7	0.4	1.1	89.8	82.9	94.2	<0.001
Placebo	1302	89	6.8	5.5	8.3				
G2									
HRV	2572	14	0.5	0.3	0.9	58.3	10.1	81.0	0.020
Placebo	1302	17	1.3	0.8	2.1				
G3									
HRV	2572	3	0.1	0.0	0.3	84.8	41.0	97.3	0.002
Placebo	1302	10	0.8	0.4	1.4				
G4									
HRV	2572	6	0.2	0.1	0.5	83.1	55.6	94.5	<0.001
Placebo	1302	18	1.4	0.8	2.2				
G9									
HRV	2572	38	1.5	1.0	2.0	72.9	59.3	82.2	<0.001
Placebo	1302	71	5.5	4.3	6.8				
Pooled Non G1 (G2, G3, G4, G9, GX)									
HRV	2572	62	2.4	1.9	3.1	72.9	62.9	80.5	<0.001
Placebo	1302	116	8.9	7.4	10.6				

Source: Appendix Table IVB and VA
N = number of subjects included in each group
n (%) = number(percentage) of subjects reporting at least one specified RV GE episode in each group
GX = G12
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value=two-sided Fisher's exact test (significant level of α=0.05)

7.2.7. Vaccine efficacy against all cause GE

Table 22 presents the efficacy of the HRV vaccine against all cause GE episodes during the combined efficacy period.

- The percentage of subjects reporting all cause GE was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against all cause GE was 14.2% [95% CI: 5.4%; 22.3%] (Table 22).

- The percentage of subjects reporting all cause GE rated as severe (Vesikari score ≥11 points) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against all cause GE rated as severe was 49.6% [95% CI: 39.8%; 57.8%] (Table 22).

- The percentage of subjects who were hospitalized due to GE was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against hospitalization due to GE was 71.5% [95% CI: 53.4%; 82.9%] (Table 22).

Table 22 Percentage of subjects reporting all cause GE episodes and vaccine efficacy from 2 weeks from 2 weeks after Dose 2 up to Visit 7 for all countries - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
All-cause GE									
HRV	2572	1096	42.6	40.7	44.6	14.2	5.4	22.3	<0.001
Placebo	1302	647	49.7	46.9	52.4				
All cause severe GE (Vesikari score ≥11 points)									
HRV	2572	256	10.0	8.8	11.2	49.6	39.8	57.8	<0.001
Placebo	1302	257	19.7	17.6	22.0				
All cause GE requiring hospitalization									
HRV	2572	27	1.0	0.7	1.5	71.5	53.4	82.9	<0.001
Placebo	1302	48	3.7	2.7	4.9				

Source: Appendix Table IVB and VA
N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one specified GE episode regardless of any cause in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

7.2.8. Vaccine efficacy against RV GE by serological status for IgA antibody concentration at Visit 3

Supplement 24 presents the VE against any RV GE caused by the circulating wild-type RV during the combined efficacy period according to the serological status for anti-rotavirus IgA antibodies at Visit 3. Supplement 25 presents the VE against severe (Vesikari score ≥11 points) RV GE caused by the circulating wild-type RV during the combined efficacy period according to the serological status for anti-rotavirus IgA antibodies at Visit 3.

It should be noted that anti-rotavirus IgA antibody results were available only for a subset of the efficacy cohort.

- Among the seronegative (for anti-rotavirus IgA antibody) subjects, the percentage of subjects reporting any RV GE was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value = 0.025). The VE against any RV GE was 64.9% [95% CI: 3.4%; 90.9%].

- Overall, since IgA response was evaluated only in a subset of subjects, it was difficult to draw a conclusion on correlation between seroconversion rate and VE.

7.2.9. Vaccine efficacy against RV GE by feeding criteria

Supplement 26 presents the efficacy of the HRV vaccine against any RV GE episode caused by the circulating wild-type RV during the combined efficacy period by feeding criteria. Supplement 27 presents the efficacy of the HRV vaccine against severe RV GE episode (Vesikari score ≥11 points) caused by the circulating wild-type RV during the combined efficacy period by feeding criteria.

The VE estimates were consistent between children who were breast-fed at the time of at least one dose of HRV vaccine and children who were not breast-fed at any dose.

7.2.10. Vaccine efficacy against RV GE scored using the Clark scale

Supplement 28 presents a summary of intensity of GE and RV GE episodes using the Clark scale reported during the combined efficacy period. Supplement 29 presents the distribution of Clark score for RV GE episodes reported during the combined efficacy period. Supplement 30 to Supplement 35 present the characteristics of RV GE episodes using the Clark scale reported during the combined efficacy period. Supplement 36 presents the characteristics of GE episodes using the Clark scale reported during the combined efficacy period.

Supplement 37 presents the efficacy of the HRV vaccine against severe RV GE according to the Clark scale during the combined efficacy period. Supplement 38 and Supplement 39 present the efficacy of the HRV vaccine against RV GE with a score ≥ a specific value on the Clark scale during the combined efficacy period.

Supplement 40 presents the efficacy of the HRV vaccine against severe RV GE using the Clark scale, by RV serotype during the combined efficacy period.

- When the RV GE episodes were scored using the Clark scale, 3.5% of the RV GE episodes in the HRV group and 14.7% of the RV GE episodes in the placebo group were rated as severe (Clark score >16 points) (Supplement 28).
- Comparing the Vesikari and Clark scales, there were more severe RV GE when using Vesikari scale (score ≥11 points) (24 in the HRV group and 127 in the placebo group) as compared to the Clark scale (score >16 points) (three in the HRV group and 30 in the placebo group). Despite these differences in the two scales, the VE against severe RV GE was similar.

7.2.11. Vaccine efficacy by country

Supplement 41 presents the number of RV GE episodes reported by G serotype and P genotype and by country, during the combined efficacy period.

Supplement 42 presents the VE against any RV GE, by country, during the combined efficacy period. Supplement 43 presents the VE against severe RV GE, by country, during the combined efficacy period. Supplement 44 presents VE against RV GE episodes requiring medical attention, by country, during the combined efficacy period.

Supplement 45 presents the efficacy of the HRV vaccine against all cause GE episodes, by country during the combined efficacy period. Supplement 46 presents the efficacy of the HRV vaccine against all cause severe (Vesikari score ≥ 11 points) GE episodes, by country during the combined efficacy period.

Supplement 47 presents the efficacy of the HRV vaccine against severe RV GE using the Clark scale, by country.

- Due to the smaller sample size in some countries (and consequently fewer RV GE episodes), the difference between groups did not reach statistical significance.
- The percentage of subjects reporting any and severe (Vesikari score ≥11 points) RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the placebo group in Finland where a sufficiently large sample size was enrolled (N = 2849 in the ATP cohort for efficacy). In Finland, The VE against severe RV GE was 90.9% [95% CI: 85.4%; 94.5%] which is consistent with results for overall efficacy (Supplement 43).

7.3. Vaccine efficacy during the second efficacy period

The ATP cohort for efficacy during the second efficacy period consisted of 3848 subjects (2554 subjects in the HRV group and 1294 subjects in the placebo group).

Table 23 presents the VE during the second efficacy period.

Supplement 48 to Supplement 84 present the results during the second efficacy period.

- The percentage of subjects who reported severe (Vesikari score ≥ 11 points) RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE was 85.6% [95% CI: 75.8%; 91.9%] (Table 23).
- The percentage of subjects who reported severe RV GE episodes caused by G1 wild-type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by G1 wild-type was 96.5% [95% CI: 86.2%; 99.6%] (Table 23).
- The percentage of subjects who reported severe RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was 80.8% [95% CI: 63.7%; 90.4%] (Table 23).
- The percentage of subjects who were hospitalized due to RV GE was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against hospitalization due to RV GE was 92.2% [95% CI: 65.6%; 99.1%] (Table 23).
- The percentage of subjects reporting any RV GE requiring medical attention was significantly lower in the HRV group when compared to the placebo group (two

sided Fisher's exact P-value <0.001). The VE against any RV GE requiring medical attention was 76.2% [95% CI: 63.0%; 85.0%] (Table 23).

- The percentage of subjects who reported any RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE was 71.9% [95% CI: 61.2%; 79.8%] (Table 23).

- The percentage of subjects who reported any RV GE caused by G1 wild-type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by G1 wild-type was 83.5% [95% CI: 69.3%; 91.7%] (Table 23).

- The percentage of subjects who reported any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was 68.2% [95% CI: 52.6%; 78.9%] (Table 23).

Table 23 Percentage of subjects reporting any and severe RV GE episodes and vaccine efficacy from during the second efficacy period - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95% CI			95% CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
Any RV GE due to circulating wild-type RV									
HRV	2554	61	2.4	1.8	3.1	71.9	61.2	79.8	<0.001
Placebo	1294	110	8.5	7.0	10.2				
Severe* RV GE due to circulating wild-type RV									
HRV	2554	19	0.7	0.4	1.2	85.6	75.8	91.9	<0.001
Placebo	1294	67	5.2	4.0	6.5				
Any RV GE due to wild-type G1									
HRV	2554	14	0.5	0.3	0.9	83.5	69.3	91.7	<0.001
Placebo	1294	43	3.3	2.4	4.5				
Severe* RV GE due to wild-type G1									
HRV	2554	2	0.1	0.0	0.3	96.5	86.2	99.6	<0.001
Placebo	1294	29	2.2	1.5	3.2				
Any RV GE due to non-G1 types									
HRV	2554	42	1.6	1.2	2.2	68.2	52.6	78.9	<0.001
Placebo	1294	67	5.2	4.0	6.5				
Severe* RV GE due to non-G1 types									
HRV	2554	14	0.5	0.3	0.9	80.8	63.7	90.4	<0.001
Placebo	1294	37	2.9	2.0	3.9				
Hospitalization due to RV GE									
HRV	2554	2	0.1	0.0	0.3	92.2	65.6	99.1	<0.001
Placebo	1294	13	1.0	0.5	1.7				
RV GE requiring medical attention									
HRV	2554	31	1.2	0.8	1.7	76.2	63.0	85.0	<0.001
Placebo	1294	66	5.1	4.0	6.4				

Source: Appendix Table IVB and VA

*episodes with score ≥ 11 points on Vesikari scale

P-value = two-sided Fisher's exact test (significant level of α=0.05)

N = number of subjects included in each group

n (%) = number(percentage) of subjects with at least one specified RV GE episode reported in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

7.4. Total vaccinated cohort

The total vaccinated cohort was used to evaluate VE against RV GE occurring from Dose 1 up to Visit 7. Supplement 85 to Supplement 126 present the results during the period from Dose 1 to Visit 7.

- Efficacy estimates for the period from Dose 1 up to Visit 7 (mean duration: 20 months in each study group) were consistent with results of the primary analysis on the ATP cohort for efficacy for the period from 2 weeks after dose 2 up to Visit 7. The results indicated that HRV vaccine was protective starting from Dose 1 onwards.
- The percentage of subjects who reported severe (Vesikari score ≥ 11 points) RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE was 90.7% [95% CI: 85.6%; 94.3%] (Supplement 112).

- The percentage of subjects who reported severe RV GE episodes caused by G1 wild-type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by G1 wild-type was 96.5% [95% CI: 90.5%; 99.1%] (Supplement 116).
- The percentage of subjects who reported severe RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against severe RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was 88.3% [95% CI: 80.0%; 93.5%] (Supplement 116).
- The percentage of subjects who were hospitalized due to RV GE was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against hospitalization due to RV GE was 95.9% [95% CI: 83.7%; 99.5%] (Supplement 124).
- The percentage of subjects who reported any RV GE episodes that required medical attention was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE requiring medical attention was 84.4% [95% CI: 77.8%; 89.2%] (Supplement 126).
- The percentage of subjects who reported any RV GE caused by the circulating wild-type RV was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE was 79.4% [95% CI: 73.4%; 84.1%] (Supplement 109).
- The percentage of subjects who reported any RV GE caused by G1 wild-type was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by G1 wild-type was 89.9% [95% CI: 83.2%; 94.3%] (Supplement 111).
- The percentage of subjects who reported any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was significantly lower in the HRV group when compared to the placebo group (two sided Fisher's exact P-value <0.001). The VE against any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12) was 73.9% [95% CI: 64.5%; 81.0%] (Supplement 111).
- From Dose 1 of HRV vaccine or placebo up to Visit 7, G1P[8] vaccine strain was detected in the stools of five GE episodes from 5 subjects (all in the HRV group) where one GE episode reported a mixed strain (G1P[8] vaccine strain, G9P[8] wild-type) (Supplement 85). All of these episodes were reported during the period from Dose 1 up to 2 weeks post Dose 2 of HRV vaccine (Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on the RV strain detected in stool samples). [redacted] The 4 GE episodes with only G1P[8] vaccine strain detected in the stools were excluded from the efficacy analysis; the GE episode with mixed strain (G1P[8] vaccine strain, G9P[8] wild-type) was included in the efficacy analysis for the total vaccinated cohort from Dose 1 up to Visit 7.

7.5. Efficacy conclusions

- Two doses of GSK Biologicals' HRV vaccine showed consistent and high efficacy over the combined efficacy period from 2 weeks post Dose 2 up to Visit 7 at the end of the second RV season.
- Two doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccines were found to be highly effective during the combined efficacy period against:
  - Severe RV GE caused by the circulating wild-type RV. The VE was 90.4% [95% CI: 85.1%; 94.1%].
  - Severe RV GE caused by G1 wild-type. The VE was 96.4% [95% CI: 90.4%; 99.1%].
  - Severe RV GE caused by non G1 types (G2, G3, G4, G9 and G12). The VE was 87.7% [95% CI: 78.9%; 93.2%].
  - Severe RV GE caused by G2 type. The VE was 85.5% [95% CI: 24.0%; 98.5%].
  - Severe RV GE caused by G3 type. The VE was 93.7% [95%CI: 52.8%; 99.9%].
  - Severe RV GE caused by G4 type. The VE was 95.4% [95%CI: 68.3%; 99.9%].
  - Severe RV GE caused by G9 type. The VE was 85.0% [95% CI: 71.7%; 92.6%].
  - Hospitalization due to RV GE caused by circulating wild-type RV. The VE was 96.0% [95% CI: 83.8%; 99.5%].
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention. The VE was 83.8% [95% CI: 76.8%; 88.9%].
  - Any RV GE caused by the circulating wild-type RV. The VE was 78.9% [95% CI: 72.7%; 83.8%].
  - Any RV GE due to G1 wild-type. The VE was 89.8% [95% CI: 82.9%; 94.2%].
  - Any RV GE caused by non G1 types (G2, G3, G4, G9 and G12). The VE was 72.9% [95% CI: 62.9%; 80.5%].
- Two doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccines were found to be highly effective during the second efficacy period against:
  - Severe RV GE caused by the circulating wild-type RV. The VE was 85.6% [95% CI: 75.8%; 91.9%].
  - Severe RV GE episodes caused by G1 wild-type. The VE was 96.5% [95% CI: 86.2%; 99.6%].
  - Severe RV GE caused by non-G1 types (G2, G3, G4, G9 and G12). The VE was 80.8% [95% CI: 63.7%; 90.4%].
  - Hospitalization due to RV GE caused by circulating wild-type RV. The VE was 92.2% [95% CI: 65.6%; 99.1%].
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention. The VE was 76.2% [95% CI: 63.0%; 85.0%].

- Any RV GE caused by the circulating wild-type RV. The VE was 71.9% [95% CI: 61.2%; 79.8%].
- Any RV GE due to G1 wild-type. The VE was 83.5% [95% CI: 69.3%; 91.7%].
- Any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12). The VE was 68.2% [95% CI: 52.6%; 78.9%].

8. IMMUNOGENICITY RESULTS

8.1. Data sets analyzed

The analyses of immunogenicity of childhood vaccinations in Finland and Italy were performed on the ATP cohort for immunogenicity (primary analysis) and on the total vaccinated cohort for the immunogenicity and reactogenicity subset. Section 5.9.3 for the definition of the cohorts identified for analyses and Section 6.2.3.1 for eligibility for analyses.

8.2. ATP cohort for immunogenicity

8.2.1. Post Dose 2 and 3 immunogenicity of childhood vaccinations in Finland and Italy

The immunogenicity of the childhood vaccinations was assessed post Dose 2 (Visit 3) and post Dose 3 (Visit 5/6) of the primary vaccination schedule in Italy and Finland.

8.2.1.1. Antibody response to diphtheria toxoid and tetanus toxoid

Table 24 and Table 25 present the seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post Dose 2 (Visit 3) and 3 (Visit 5/6) of the routine childhood vaccination in Italy and Finland, respectively. Supplement 127 to Supplement 130 present RCC for post Dose 3 anti-diphtheria and anti-tetanus antibody concentrations in Italy and Finland.

- In Finland and Italy, the seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies were similar in both groups.

Table 24 Seroprotection rates and GMCs for anti-Diphtheria and anti-Tetanus antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Diphtheria	HRV	PII (M3)	13	13	100	75.3	100	2.223	1.358	3.640
		PIII (M9)	12	12	100	73.5	100	6.738	4.313	10.529
	Placebo	PII (M3)	9	9	100	66.4	100	2.876	1.950	4.240
		PIII (M9)	9	9	100	66.4	100	7.395	4.539	12.049
anti-Tetanus	HRV	PII (M3)	13	13	100	75.3	100	2.278	1.395	3.719
		PIII (M9)	12	12	100	73.5	100	5.766	3.656	9.095
	Placebo	PII (M3)	9	9	100	66.4	100	2.765	1.363	5.608
		PIII (M9)	9	9	100	66.4	100	6.453	3.392	12.273

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PII (M3) = post dose 2 of routine childhood vaccination (Visit 3); PIII (M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Table 25 Seroprotection rates and GMCs for anti-Diphtheria and anti-Tetanus antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Diphtheria	HRV	PII (M3)	167	153	91.6	86.3	95.3	0.569	0.470	0.689
		PIII (M10)	164	163	99.4	96.6	100	2.809	2.418	3.263
	Placebo	PII (M3)	105	99	94.3	88.0	97.9	0.550	0.441	0.687
		PIII (M10)	101	101	100	96.4	100	2.493	2.135	2.911
anti-Tetanus	HRV	PII (M3)	167	167	100	97.8	100	1.206	1.043	1.394
		PIII (M10)	164	164	100	97.8	100	5.583	5.043	6.181
	Placebo	PII (M3)	105	105	100	96.5	100	1.351	1.133	1.611
		PIII (M10)	101	101	100	96.4	100	4.976	4.378	5.656

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

8.2.1.2. Antibody response to PT, FHA and PRN

Table 26 and Table 27 present the seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination in Italy and Finland, respectively. Supplement 131 to Supplement 136 present post Dose 3 RCCs for anti-PT, anti-FHA and anti-PRN antibody concentrations in Finland and Italy.

- In Finland and Italy, the seropositivity rates for anti-PT, anti-FHA and anti-PRN antibodies were similar in both groups.
- In Finland and Italy, GMCs for anti-PT, anti-FHA and anti-PRN antibodies were similar in both groups; except for post Dose 3 anti-PT antibody in Finland where GMC tended to be higher in the HRV group (See Section 8.2.1.6).

Table 26 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity

				≥ 5 EL.U/ML				GMC		
						95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-PT	**HRV**	**PII (M3)**	13	13	100	75.3	100	47.3	25.2	89.0
		PIII (M9)	12	12	100	73.5	100	69.7	38.6	125.8
	Placebo	**PII (M3)**	8	8	100	63.1	100	44.0	27.4	70.6
		PIII (M9)	9	9	100	66.4	100	79.7	63.1	100.8
anti-FHA	**HRV**	**PII (M3)**	13	13	100	75.3	100	241.8	152.6	383.2
		PIII (M9)	12	12	100	73.5	100	504.4	323.1	787.5
	Placebo	**PII (M3)**	9	9	100	66.4	100	152.7	99.6	234.2
		PIII (M9)	9	9	100	66.4	100	531.3	392.9	718.3
anti-PRN	**HRV**	**PII (M3)**	13	13	100	75.3	100	124.0	59.8	257.3
		PIII (M9)	12	12	100	73.5	100	285.2	174.3	466.8
	Placebo	**PII (M3)**	9	9	100	66.4	100	168.9	117.7	242.4
		PIII (M9)	9	9	100	66.4	100	348.6	235.3	516.4

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M9) = post dose 3 of routine childhood vaccination (Visit 5/ 6)

Table 27 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity

				≥ 5 EL.U/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-PT	HRV	PII (M3)	167	167	100	97.8	100	50.9	46.1	56.3
		PIII (M10)	164	164	100	97.8	100	96.1	88.3	104.5
	Placebo	PII (M3)	104	104	100	96.5	100	47.8	42.1	54.4
		PIII (M10)	101	101	100	96.4	100	81.7	72.6	91.8
anti-FHA	HRV	PII (M3)	167	167	100	97.8	100	179.0	160.1	200.1
		PIII (M10)	164	164	100	97.8	100	551.3	503.3	604.0
	Placebo	PII (M3)	105	105	100	96.5	100	173.8	152.7	197.9
		PIII (M10)	101	101	100	96.4	100	476.1	421.7	537.4
anti-PRN	HRV	PII (M3)	166	164	98.8	95.7	99.9	77.2	64.2	93.0
		PIII (M10)	164	164	100	97.8	100	307.7	275.2	343.9
	Placebo	PII (M3)	103	102	99.0	94.7	100	97.9	78.2	122.5
		PIII (M10)	101	101	100	96.4	100	303.3	262.4	350.6

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

8.2.1.3. Antibody response to HBs

Table 28 and Table 29 present the seroprotection rates and GMCs for anti-HBs antibodies post Dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination in Italy and Finland, respectively. Supplement 137 and Supplement 138 present post Dose 3 RCCs for anti-HBs antibody concentrations in Italy and Finland.

- In Finland and Italy, the seroprotection rates and GMCs for anti-HBs antibodies were similar in both groups.

Table 28 Seroprotection rates and GMCs for anti-HBs antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-HBS	HRV	PII (M3)	11	11	100	71.5	100	711.9	272.9	1857.1
		PIII (M9)	12	12	100	73.5	100	4030.4	1759.8	9230.6
	Placebo	PII (M3)	8	7	87.5	47.3	99.7	282.6	60.9	1312.8
		PIII (M9)	8	7	87.5	47.3	99.7	2185.8	246.1	19413.3

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Table 29 Seroprotection rates and GMCs for anti-HBS antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-HBS	HRV	PII (M3)	166	162	97.6	93.9	99.3	431.6	345.3	539.4
		PIII (M10)	163	163	100	97.8	100	6638.9	5529.8	7970.5
	Placebo	PII (M3)	105	98	93.3	86.7	97.3	399.7	286.0	558.5
		PIII (M10)	101	101	100	96.4	100	5577.3	4270.6	7283.7

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

8.2.1.4. Antibody response to poliovirus types 1, 2 and 3

Table 30 and Table 31 present the seroprotection rates and GMTs for anti-Polio 1, anti-Polio 2 and anti-Polio 3 antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination in Italy and Finland, respectively. Supplement 139 to Supplement 144 present post-Dose 3 RCC for anti-poliovirus 1, anti-poliovirus 2, anti-poliovirus 3 antibody titers in Italy and Finland.

- In Finland and Italy, the seroprotection rates for anti-Polio 1, anti-Polio 2 and anti-Polio 3 antibodies were similar in both groups.

- In Finland and Italy, GMTs for anti-polio 1, anti-polio 2 and anti-polio-3 antibodies were similar in both groups; except for post Dose 3 anti-polio 2 antibody in Finland where GMT tended to be higher in the HRV group (See Section 8.2.1.6).

Table 30 Seroprotection rates and GMTs for anti-Polio 1, anti-Polio 2 and anti-Polio 3 antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity

				≥ 8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1	HRV	PII (M3)	5	5	100	47.8	100	415.8	190.3	908.7
		PIII (M9)	3	3	100	29.2	100	6502.0	2406.0	17570.7
	Placebo	PII (M3)	5	5	100	47.8	100	337.8	115.7	986.2
		PIII (M9)	4	4	100	39.8	100	3158.4	929.8	10728.8
anti-Polio 2	HRV	PII (M3)	4	4	100	39.8	100	107.6	9.3	1241.9
		PIII (M9)	4	4	100	39.8	100	5792.6	1922.5	17453.4
	Placebo	PII (M3)	6	6	100	54.1	100	256.0	153.1	428.2
		PIII (M9)	4	4	100	39.8	100	4466.8	1741.6	11456.0
anti-Polio 3	HRV	PII (M3)	4	3	75.0	19.4	99.4	234.8	1.9	28973.7
		PIII (M9)	4	4	100	39.8	100	4466.6	648.2	30780.4
	Placebo	PII (M3)	6	6	100	54.1	100	304.4	44.0	2107.4
		PIII (M9)	4	4	100	39.8	100	2655.9	197.0	35804.4

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with titre above the cut-of
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Table 31 Seroprotection rates and GMTs for anti-Polio 1, anti-Polio 2 and anti-Polio 3 antibodies post dose 2 (Visit 3) and 3 (Visit 5/ 6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity

				≥ 8 ED_{50}				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1	HRV	PII (M3)	151	132	87.4	81.0	92.3	47.3	36.2	61.9
		PIII (M10)	136	136	100	97.3	100	1072.1	865.3	1328.4
	Placebo	PII (M3)	98	85	86.7	78.4	92.7	37.2	26.9	51.3
		PIII (M10)	94	94	100	96.2	100	896.9	689.3	1167.0
anti-Polio 2	HRV	PII (M3)	154	97	63.0	54.8	70.6	11.9	9.7	14.7
		PIII (M10)	133	133	100	97.3	100	589.7	443.2	784.5
	Placebo	PII (M3)	98	60	61.2	50.8	70.9	11.4	9.0	14.6
		PIII (M10)	88	88	100	95.9	100	319.4	221.6	460.5
anti-Polio 3	HRV	PII (M3)	151	139	92.1	86.5	95.8	83.2	62.6	110.7
		PIII (M10)	129	129	100	97.2	100	1499.4	1153.4	1949.2
	Placebo	PII (M3)	94	82	87.2	78.8	93.2	49.5	34.3	71.6
		PIII (M10)	82	81	98.8	93.4	100	1028.4	714.8	1479.6

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with titre above the cut-of
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/ 6)

8.2.1.5. Antibody response to PRP

Table 32 and Table 33 present the seroprotection rates and GMCs for anti-PRP antibodies post dose 2 (Visit 3) and 3 (Visit 5/ 6) of routine childhood vaccination in Italy and Finland, respectively. Supplement 145 and Supplement 146 present post Dose 3 RCCs for anti-PRP antibody concentrations in Italy and Finland.

- In Finland and Italy, the percentage of subjects with anti-PRP concentration ≥ 0.15 μg/ml and ≥ 1.0 μg/ml for anti-PRP antibodies were similar for both groups.

- In Finland and Italy, GMCs for anti-PRP antibodies were similar in both groups; except for post Dose 3 anti-PRP antibody in Finland where GMC tended to be higher in the HRV group (See Section 8.2.1.6).

Table 32 Seroprotection rates and GMCs for anti-PRP antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity

				≥ 0.15 UGR/ML				≥ 1 UGR/ML				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	HRV	PII (M3)	13	12	92.3	64.0	99.8	9	69.2	38.6	90.9	2.313	0.750	7.137
		PIII (M9)	12	12	100	73.5	100	12	100	73.5	100	13.191	6.450	26.980
	Placebo	PII (M3)	9	8	88.9	51.8	99.7	4	44.4	13.7	78.8	1.905	0.347	10.461
		PIII (M9)	9	9	100	66.4	100	9	100	66.4	100	14.265	4.464	45.580

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Table 33 Seroprotection rates and GMCs for anti-PRP antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity

				≥ 0.15 UGR/ML				≥ 1 UGR/ML				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	HRV	PII (M3)	167	162	97.0	93.2	99.0	96	57.5	49.6	65.1	1.671	1.326	2.107
		PIII (M10)	163	163	100	97.8	100	158	96.9	93.0	99.0	16.051	13.429	19.186
	Placebo	PII (M3)	105	96	91.4	84.4	96.0	57	54.3	44.3	64.0	1.365	1.002	1.860
		PIII (M10)	101	101	100	96.4	100	100	99.0	94.6	100	11.752	9.372	14.736

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number(percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

8.2.1.6. Evaluation of the differences between groups

Supplement 147 to Supplement 168 present the asymptotic standardized 95% CI on the difference in the post Dose 3 seropositivity/seroprotection rates for antibodies to each antigen in the childhood vaccinations between groups in Finland and Italy.

- For Finland and Italy, a statistically significant difference was not detected between the two groups for post Dose 3 seropositivity rate/seroprotection rate to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP since the two-sided asymptotic standardized 95% CIs for the treatment differences (placebo minus HRV) contain the value zero.

Supplement 169 to Supplement 188 present the 95% CI for the ratios of post Dose 3 GMCs/ GMTs for antibodies to each antigen in the childhood vaccinations between the groups.

- For Finland and Italy, a statistically significant difference was not detected between the two groups for post Dose 3 GMCs/GMTs of antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3, and PRP since the 95% CI for the ratios of GMC/GMT (placebo over HRV) for each antibody contain the value one, except for
  - anti-PT antibody in Finland (higher response for the HRV vaccine group).
  - anti-poliovirus type 2 antibody in Finland (higher response for the HRV vaccine group).
  - anti-PRP antibody in Finland (higher response for the HRV vaccine group).

8.3. Total vaccinated cohort for the immunogenicity and reactogenicity subset

Supplement 189 to Supplement 198 present immunogenicity results for the total vaccinated cohort for the immunogenicity and reactogenicity subset in Italy and Finland.

In Italy and Finland, the immunogenicity results obtained in the total vaccinated cohort for the immunogenicity and reactogenicity subset were consistent with those obtained in the ATP cohort for immunogenicity.

8.4. Immunogenicity conclusion

- GSK Biologicals' HRV vaccine did not appear to impact on the immunogenicity of any of the antigens contained in the co-administered childhood vaccinations in Finland and Italy.

9. SAFETY RESULTS

9.1. Data sets analyzed

The analyses of safety were performed on the total vaccinated cohort. Section 5.9.3 for the definition of the cohorts identified for analyses and Section 6.2.3.1 for eligibility for analyses.

9.2. Serious adverse events

Table 34 presents the percentage of subjects with SAEs/IS occurring from Dose 1 of HRV vaccine/ placebo up to Visit 7

From Dose 1 of HRV vaccine/placebo up to Visit 7,

- 11.0% [95%CI: 9.8%; 12.2%] subjects in the HRV group and 13.1% [95%CI: 11.3%; 15.0%] subjects in the placebo group reported at least one SAE (P-value = 0.051).
- Three subjects reported IS (2 in HRV group and 1 in placebo group). One subject from the HRV group reported IS, assessed as related to vaccination, on Day 8 post Dose 2 of the HRV vaccine (Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on this case). The 2 IS reported after Visit 5 were assessed as not causally related to vaccination. The observed Risk Difference (HRV minus placebo) for IS reported from Dose 1 of HRV vaccine/placebo up to Visit 7 was 0% [95% CI: -0.35%; 0.21%], P-value = 0.988.

Table 34 Percentage of subjects with SAEs/Intussusceptions occurring from Dose 1 of HRV vaccine/Placebo up to visit 7 – Pooled countries – Total vaccinated cohort

	HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
			95% CI				95% CI			95% CI*		
	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one SAE	290	11.0	9.8	12.2	176	13.1	11.3	15.0	-2.10	-4.31	0.01	0.051
At least one IS	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988

Data source = Appendix table IIC
N=number of subjects having received at least one dose of HRV vaccine/placebo
n (%) = number (percentage) of subjects reporting at least one SAE/IS between the day of administration of dose 1 of HRV vaccine/Placebo up to Visit 7 (or last study contact if Visit 7 not performed)
95% CI = exact 95% confidence interval
95% CI* = asymptotic standardised 95% confidence interval on the risk difference
L.L. = lower limit, U.L. = upper limit
P-value = results of the comparison between groups of percentage of subjects reporting the specified AE from dose 1 of HRV vaccine/Placebo up to visit 7, by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 have been used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 201 presents the percentage of subjects with SAEs occurring from Dose 1 of the HRV vaccine/placebo up to Visit 7, classified by MedDRA primary system organ class (SOC). Supplement 202 presents the percentage of subjects with SAEs occurring from Dose 1 of the HRV vaccine/placebo up to Visit 7, classified by MedDRA primary SOC and PT.

Putative statistically significant findings (based on a predefined exploratory P-value < 0.05 significance level) should be interpreted cautiously since the observed imbalances are likely to occur by chance alone due to the number of comparisons performed without multiplicity adjustment.

When SAEs from Dose 1 of HRV vaccine/placebo up to Visit 7 were classified according to the MedDRA SOCs/PTs, potential imbalance between the HRV group and the placebo group was seen for the following SAEs:

- Potential imbalance in favour of HRV vaccine were noted for SAEs classified under the PTs ‘Gastroenteritis’, ‘Gastroenteritis rotavirus’, ‘Head injury’ and ‘Testicular torsion’. (Supplement 201 and Supplement 202). Potential imbalance in favour of HRV vaccine were noted for SAEs classified under the SOC ‘Infections and infestations’. Since the imbalance between the groups was mainly driven by events classified under PTs that are linked or related to "Gastroenteritis disease", the observed difference most likely reflects efficacy of the HRV vaccine in preventing GE related symptoms. The two cases (in the placebo group) reported for each SAE classified under the PTs ‘Head injury’ and ‘Testicular torsion’ is likely a chance finding and not clinically relevant.
- Potential imbalance in favour of the placebo was noted for SAE classified under the PT ‘Pneumonia’. 28 cases of pneumonia in total were reported from Dose 1 of the HRV vaccine/placebo up to Visit 7 but majority of cases, (19 out of 28 cases) were reported after Visit 5. From the HRV group, only one case was reported within 30 days after vaccination (Supplement 201 and Supplement 202).

Individual cases under MedDRA PT pneumonia were reviewed by sponsor physicians. Clinical review of individual cases by the sponsor physician gave no evidence of clinically relevant findings indicating that the potential imbalance was possibly a chance finding. It should be noted that the potential imbalance between treatment groups based on the specific MedDRA PT pneumonia was not observed for unsolicited AEs reported from Day 0 to Day 30 after any HRV vaccine/placebo doses. (Refer to the Study report for Study 102247 (Rota-036) dated 03 March 2006 for information on unsolicited AEs reported from Day 0 to Day 30 after any HRV vaccine/placebo doses classified according to the MedDRA SOCs/PTs).

9.2.1. Fatal events

No fatal events were reported from Dose1 of HRV vaccine/ placebo up to Visit 7.

9.3. Adverse Events Leading to Premature Discontinuation of Study Vaccine and/ or Study

Supplement 199 and Supplement 200 present a summary of subjects who dropped-out due to SAEs and AEs from Dose 1 of the HRV vaccine/ placebo up to Visit 7, respectively.

Five subjects withdrew due to non-fatal SAEs (one subject in the HRV group and four subjects in the placebo group). All SAEs leading to drop out were considered by the investigators to be not related to vaccination.

- One subject in the HRV group experienced a SAE (primitive neuroectodermal tumor) that led to his drop-out. Four subjects in the placebo group experienced SAEs (Convulsion, Lissencephaly, Epilepsy and Infantile spasms, respectively) that led to drop-out.

Ten subjects withdrew due to non-serious AEs (seven subjects in the HRV group and three subjects in the placebo group).

- Seven subjects in the HRV group experienced AEs (Bronchospasm reported in two subjects, Gastroenteritis, Hypersensitivity, Haematochezia, Constipation and Irritability) that led to his/ her drop-out. Three subjects in the placebo group experienced AEs (Motor dysfunction, Gastrointestinal disorder and Varicella, respectively) that led to his/ her drop-out.

9.4. Concomitant medications/ vaccinations

Supplement 203 presents the percentage of doses and of subjects who started taking at least one concomitant medication during the study period.

- The overall percentage of subjects who started taking at least one concomitant medication during the study period was similar for both groups.
- The overall percentage of subjects who received any antipyretic, prophylactic antipyretic or any antibiotic during the study period was similar for both groups.

9.5. Safety conclusion

There was no evidence for a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 7.

10. DISCUSSION AND CONCLUSIONS

This study was conducted in Czech Republic, Finland, France, Germany, Italy and Spain to assess the efficacy, immunogenicity and safety of two doses of HRV vaccine that was given concomitantly with the childhood vaccinations.

From the 3994 subjects enrolled in this study, a total of 3874 subjects (2572 in the HRV group and 1302 in the placebo group) were included in the ATP cohort for efficacy

during the first efficacy period as well as the ATP cohort for efficacy during the combined efficacy period. 3848 subjects (2554 in the HRV group and 1294 in the placebo group) were included in the ATP cohort for efficacy during the second efficacy period.

During the first efficacy period, it was observed that the vaccine was highly effective in preventing severe RV GE (VE: 95.8% [95% CI: 89.6%; 98.7%]) caused by circulating wild-type RV. During the second efficacy period, the HRV vaccine was efficacious in preventing severe RV GE (VE: 85.6% [95% CI: 75.8%; 91.9%]).The results during the combined efficacy period were in the same range with excellent VE against severe RV GE (90.4% [95% CI: 85.1%; 94.1%]).

High VE of 96.0% [95% CI: 83.8%; 99.5%] was observed in preventing hospitalizations due to RV GE episodes and a VE of 83.8% [95% CI: 76.8%; 88.9%] was observed in reducing any RV GE episodes requiring medical attention during the combined efficacy period.

The main circulating strains during the first and second efficacy periods were G1, G4 and G9 types and G1, G2 and G9 types, respectively. G1 and G9 types were the two predominant strains isolated during the study period.

The vaccine was efficacious against severe RV GE caused by isolated G1 and non-G1 RV types. The VE shown against non-G1 types (G2, G3, G4, G9 and G12) was 87.7% [95% CI: 78.9%; 93.2%] during the combined efficacy period. During the clinical studies thus far including the first efficacy follow-up period in study Rota-036, a trend towards protection against G2P[4] type which is completely heterologous from the vaccine type was seen. Meta analysis of severe RV GE episodes caused by G2 type from studies Rota 004, Rota 006, Rota 007, Rota 023 and Rota-036 (first year) showed substantial protection with VE of 71.4% [95% CI: 20.1%; 91.1%] [Perez-Schael, 2005]. The VE shown against the G2 type by meta analysis was confirmed by the significant VE that has been observed against severe RV GE caused by G2 type during the second and combined efficacy period (VE: 89.9% [95% CI: 9.4%; 99.8%]) and (VE: 85.5% [95% CI: 24.0%; 98.5%]), respectively.

Two doses of the HRV vaccine given concomitantly with the childhood vaccinations in Finland and Italy did not appear to have any effect on the immunogenicity of any of the routine vaccine antigens. The seropositivity rates/seroprotection rates or GMCs/GMTs for antibodies to diphtheria, tetanus, PT, FHA, PRN, HBs, poliovirus types 1, 2 and 3 and PRP were similar between the HRV and placebo groups after three doses of childhood vaccinations.

A phase III trial involving more than 60,000 infants has proved that the HRV vaccine is not associated with an increased risk of IS as compared to the placebo [Ruiz Palacios, 2006]. Within the present trial setting, the vaccine was not associated with an increased risk of IS from Dose 1 up to Visit 7 compared to the placebo; the observed Risk Difference was 0.00% [95% CI: -0.35%; 0.21%, P-value = 0.988]. Three subjects reported IS during the study. Only one case was close to vaccination; two cases were remote from vaccination.

Overall percentages of subjects with SAEs reported from Dose 1 up to Visit 7 were similar between the HRV vaccine and placebo groups.

A potential imbalance not in favour of the HRV vaccine was observed for SAEs classified according to the MedDRA PT pneumonia from Dose 1 up to Visit 7. Clinical review of individual cases by the sponsor physician gave no evidence of clinically relevant findings indicating that the potential imbalance was possibly a chance finding. Majority of the cases were reported remotely from study vaccination during the second efficacy follow-up period.

Overall Conclusions

- Two doses of GSK Biologicals' HRV vaccine showed consistent and high efficacy over the combined efficacy period from 2 weeks post Dose 2 up to Visit 7 at the end of the second RV season.
- Two doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccines were found to be highly effective during the combined efficacy period against:
  - Severe RV GE caused by the circulating wild-type RV. The VE was 90.4% [95% CI: 85.1%; 94.1%].
  - Severe RV GE caused by G1 wild-type. The VE was 96.4% [95% CI: 90.4%; 99.1%].
  - Severe RV GE caused by non G1 types (G2, G3, G4, G9 and G12). The VE was 87.7% [95% CI: 78.9%; 93.2%].
  - Severe RV GE caused by G2 type. The VE was 85.5% [95% CI: 24.0%; 98.5%].
  - Severe RV GE caused by G3 type. The VE was 93.7% [95%CI: 52.8%; 99.9%].
  - Severe RV GE caused by G4 type. The VE was 95.4% [95%CI: 68.3%; 99.9%].
  - Severe RV GE caused by G9 type. The VE was 85.0% [95% CI: 71.7%; 92.6%].
  - Hospitalization due to RV GE caused by circulating wild-type RV. The VE was 96.0% [95% CI: 83.8%; 99.5%].
  - RV GE episodes caused by the circulating wild-type RV requiring medical attention. The VE was 83.8% [95% CI: 76.8%; 88.9%].
  - Any RV GE caused by the circulating wild-type RV. The VE was 78.9% [95% CI: 72.7%; 83.8%].
  - Any RV GE due to G1 wild-type. The VE was 89.8% [95% CI: 82.9%; 94.2%].
  - Any RV GE caused by non G1 types (G2, G3, G4, G9 and G12). The VE was 72.9% [95% CI: 62.9%; 80.5%].
- Two doses of GSK Biologicals' HRV vaccine co-administered with childhood vaccines were found to be highly effective during the second efficacy period against:
  - Severe RV GE caused by the circulating wild-type RV. The VE was 85.6% [95% CI: 75.8%; 91.9%].

- Severe RV GE episodes caused by G1 wild-type. The VE was 96.5% [95% CI: 86.2%; 99.6%].
- Severe RV GE caused by non-G1 types (G2, G3, G4, G9 and G12). The VE was 80.8% [95% CI: 63.7%; 90.4%].
- Hospitalization due to RV GE caused by circulating wild-type RV. The VE was 92.2% [95% CI: 65.6%; 99.1%].
- RV GE episodes caused by the circulating wild-type RV requiring medical attention. The VE was 76.2% [95% CI: 63.0%; 85.0%].
- Any RV GE caused by the circulating wild-type RV. The VE was 71.9% [95% CI: 61.2%; 79.8%].
- Any RV GE due to G1 wild-type. The VE was 83.5% [95% CI: 69.3%; 91.7%].
- Any RV GE caused by non-G1 types (G2, G3, G4, G9 and G12). The VE was 68.2% [95% CI: 52.6%; 78.9%].

- GSK Biologicals' HRV vaccine did not appear to impact on the immunogenicity of any of the antigens contained in the co-administered childhood vaccinations in Finland and Italy.

- There was no evidence for a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 7.

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13. APPENDICES

List of Appendices available for the study report

APPENDIX 1: INDIVIDUAL DATA LISTINGS
Since the study was blinded until study end, the individual listings present individual subject data for all subjects in study Rota-036 from Visit 1 until Visit 7.

I	Ai	Elimination codes
I	Aii	Elimination codes FU

Demography

I	B	Demography
	Ci	Dates of birth, vaccination, sampling, visits
	ICii	Reason for visit not done
	D	General medical history - physical examination
	Ei	Study conclusion
	Eii	Study conclusion FU
	Eiii	Subjects whose the code has been broken
	G	Vaccination procedure
	I	Reason for vaccine not administered
	J	Reason for non-eligibility
	K	Feedings
	L	Epidemiological data

Reactogenicity

II	Bi	Solicited general solicited symptoms
	Bii	Detailed information on gastroenteritis episodes during solicited period
	C	Unsolicited Adverse Events
	Ci	Unsolicited Adverse Events within 31-day (Days 0-30) post vaccination
	Cii	Unsolicited Adverse Events started more than 31-day (> day 30) post vaccination
	Ciii	Unsolicited Adverse Events reported before vaccination
	Di	Medication
	Dii	Concomitant vaccination

Immunogenicity

III	A	Immunogenicity

Stool analysis

V	B	Gastroenteritis stool collection results

Efficacy

V	A	Detailed information of gastroenteritis episodes during unsolicited period

APPENDIX 2: SERIOUS ADVERSE EVENTS
Appendix 2A CIOMS Narratives for Serious Adverse Events reported after Visit 5 up to Visit 7
Appendix 2B Serious Adverse Events Summary Table for SAEs reported after Visit 5 up to Visit 7

APPENDIX 3: STUDY INFORMATION
Appendix 3A Sponsor Information
Appendix 3B Protocol and protocol amendments
Appendix 3C Sample Case Report form (unique pages only)
Appendix 3D List of IECs or IRBs (plus name of committee chair if required by regulatory authority)
Appendix 3E Representative Written information for patient and sample consent forms
Appendix 3F List of investigators and other important participants in the study
Appendix 3G Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
Appendix 3H Signature of principal investigator
Appendix 3I Randomization scheme (patient identification and treatment assigned)
Appendix 3J Audit Certificate
Appendix 3K Publications based on the study
Appendix 3L Important publications referenced in the report
Appendix 3M CRFs for SAEs and withdrawals due to adverse events should be available upon request

Clintrial Eligibility Codes

Elimination from ATP cohorts for reactogenicity, immunogenicity and efficacy

1030 Study vaccine dose not administered AT ALL but subject number allocated
1040 Administration of intercurrent vaccine(s) forbidden in the protocol
1060 Randomization code broken
1070 Study vaccine dose not administered according to protocol :
- Replacement/ Wrong vaccine vial used NOT corresponding to the correct randomization group
- Subject number not in the randomization list and not requested by the sponsor (extra PID)
1500 Initially seropositive or initially unknown anti-rotavirus IgA antibody status on the day of Dose 1 of HRV vaccine or placebo for subjects included in the immunogenicity and reactogenicity subset.

Elimination from ATP cohort for reactogenicity and from ATP cohort for immunogenicity

1035 Subjects for whom solicited symptoms were not to be collected and who were not planned to be bled for all blood sampling visits

Elimination from ATP cohort for immunogenicity

2010 Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.
2040 Administration of any intercurrent medication forbidden by the protocol
2050 Underlying medical condition forbidden by the protocol
2060 Concomitant infection by rotavirus which may influence immune response (=rotavirus other than vaccine strain in GE stool samples collected up to Visit 3)
2070 Concomitant infection not related to the vaccine which may influence immune response
2080 Non compliance with vaccination schedules for HRV vaccine or placebo (dates of vaccination not corresponding to adapted protocol intervals or unknown vaccination dates)
2090 Non compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS dates)
2100 Serological results not available for the blood sample POST vaccination (including BS lost, Not Done, unable to test, absence of parallelism):
2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between eCRF and results, wrong labelling in BS)

Important remark: if code 2100 was attributed to a subject, codes 2080 and/or 2090 were not to be assigned to the same subject

Elimination from ATP cohort for efficacy – first and combined efficacy period

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 other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response

Elimination from ATP cohort for efficacy – second efficacy period

4020 Subjects not entered into the surveillance period of the second efficacy follow-up period

4500 Randomization code broken (**not assigned if code 1060 already assigned)**

Notes to Individual Data Listings

The following abbreviations are common throughout the Appendix tables:

Sub. No. : subject number
Eli MA. : eligibility in the main analysis
E : eliminated from reactogenicity and immunogenicity analyses
I : eliminated from immunogenicity analysis
Ctr. : Study centre
N : No
Y : Yes

Abbreviations which are unique to a particular appendix are presented below.

Appendix Table I.A

Elim Codes : elimination codes

Appendix Table I.B

M/F : male/female
MC : missing confirmed

Appendix Table I.C

ND : not done
VAC ND : vaccine not administered
VIS ND : visit not done
PRE : pre-vaccination
PII (M2-10) : two to ten months after Dose 2 of HRV vaccine or placebo
Reason : reason for visit not done: OTH/SAE/AEX/SAM: other/serious adverse event/non-serious adverse event/Same reason and decision as previous visit

Appendix Table I.D

Past : medical history
Current : present at the physical examination
Both : past and current

Appendix Table I.E

Elim Crit : elimination criteria during the study Y/N: Yes/No
SAE? : any serious adverse event Y/N: Yes/No
Link to an AE : withdrawal of the subject link to an adverse event Y/N: yes/no

Appendix Table I.G

According to Prot?: Administration of the vaccine according to protocol in terms of side/site/route

Type_vac
1 : vaccine not administered according to protocol: wrong side/site/route or replacement or wrong vial number
2 : Vaccine planned but not administered for a given visit
3 : Administration of a study vaccine not planned in the group

Appendix Table II

Adm?: vaccine administration N/R/S/W: not administered/replacement/study vaccine/wrong vial

Reason: reason for vaccine not administered : OTH/SAE/AEX: other/serious adverse event/non-serious adverse event

Appendix Table IIBi

G? : Any general symptom: Y/N/U/M: Yes / No / Unknown / Missing

EXP : Adverse event: Y/N: Yes / No

caus : Causality: Y/N : Yes / No

Symptoms

CO : Cough/runny nose

CO scored as: Empty/0 = no adverse event/Normal

1 = Cough/runny nose which is easily tolerated.

2 = Cough/runny nose which interferes with daily activities

3 = Cough/runny nose which prevents daily activity

DA : Diarrhoea

IR : Irritability/fussiness

IR scored as: Empty/0 = no adverse event/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

LO : Loss of appetite

LO scored as: Empty/0 = no adverse event/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.

VO : Vomiting

FE : Temperature = Body temperature in °Cs or °Fs

RTE : Route (for body temperature recording):

A = axillary

Pre vac : Pre-vaccination temperature

MC : Missing confirmed (adverse event reported but no value available)

O? : Ongoing at the end of the solicited follow-up period Y/N: Yes / No

Last day : End day of symptom if it has continued after the solicited follow-up period

Appendix Table II.C

Verbatim : Description of experience as recorded in the case report form

Keyword : Specific identification terminology linked to the MedDRA classification codes

MedDRA code: Code for MedDRA preferred term, a MedDRA adverse reaction classification system

Preferred term : Medical term assigned to the keyword/verbatim

SOC code : Pirmary System Organ Class code: a numeric code in relation with the location of the adverse event in the body

Pr. Do : Dose given prior to the adverse event

M? : Any medical advice sought: Y/N: Yes/No

ER : Emergency room
MD : Medical Doctor
HO : hospitalization
Imm pst vacc : Adverse event starting during immediate post-vaccination period (at least 30 minutes)
caus : Causality: Y/N: Yes / No
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:
1 = Mild
2 = Moderate
3 = Severe.
L/G : local or general
Out : outcome: 1 = recovered/resolved
2 = recovering/resolving
3 = not recovered/not resolved
4 = Recovered with sequelae/Resolved with sequelae
5 = died
Ser : serious adverse event: Y/N: Yes / No

Appendix Table II.Di
Prev. dose : previous vaccine dose
Rel. day of onset : day of onset of medication, relative to day of previous vaccination
Start date : date medication administration started
End date : date of end of medication
Dur (day) : duration (days)
Trade-Generic name : trade and/or generic name of medication
Modif. Trad : Modified tradename
Antibiot : antibiot Y: yes
Antipyr : Antipyretic Y: yes
Medical indic. : Medical indication for which medication was used
Proph : Prophylactic medication Y (Yes) or blank

Appendix Table II.Dii
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
Trade name : trade name of vaccine administered
Start date : date of administration of concomitant vaccine

Appendix Table III.A
cut : Cut-off of the laboratory assay
BS ND : Blood sampling not done
IR : Invalid result
QNS : Quantity of serum not sufficient

PRE : pre-vaccination
PII(M2-10) : two to ten months after Dose 2 of HRV vaccine or placebo

Appendix Table V.B

prev dose : Previous vaccine dose
Onset Day : Number of days since last vaccine dose
NEG : Negative for rotavirus
POS : Positive for rotavirus
ND : Not done
NT : Not tested
IR : Invalid result
QNS : Quantity not sufficient

Appendix Table V.A

Epi nb : Episode number of the GE
Last.dose : Previous vaccine dose
Day of onset : Number of days since last vaccine dose
Nb. of stools/day : number of looser than normal stools per day (99= missing confirmed)
Nb. of vomiting/day : number of vomiting per day (99= missing confirmed)
Temp. not taken : temperature not taken
Treat type : OR=oral, IV=intravenous, ORIV= oral and intravenous, OTH=other
MC : Missing confirmed
Med Type: Medical type
AD : Medical contact without Visit
ER : Emergency room
MD : Medical Personnel (Visit)
HO : hospitalization
NEG : Negative for rotavirus
POS : Positive for rotavirus
QNS : Quantity not sufficient
RTE : Route for recording body temperature
A : Axillary
R : Rectal

SUPPLEMENTS

PAGE

Supplement 1 Age (in months) at visit 7 or last contact, by country – Total vaccinated cohort

Country	Age at visit 7 or at last contact for year 2 if visit 7 not performed (Months)	HRV	Placebo	Total
	Parameters	Value	Value	Value
Czech republic	N	199	100	299
	Mean	22.5	22.3	22.4
	SD	1.83	2.32	2.01
	Minimum	2	7	2
	Median	23.0	23.0	23.0
	Maximum	25	25	25
Finland	N	1918	972	2890
	Mean	22.3	22.4	22.3
	SD	1.86	1.92	1.88
	Minimum	3	5	3
	Median	22.0	23.0	22.0
	Maximum	28	27	28
France	N	95	51	146
	Mean	20.2	20.4	20.3
	SD	3.00	3.03	3.00
	Minimum	3	3	3
	Median	21.0	20.0	21.0
	Maximum	24	24	24
Germany	N	190	99	289
	Mean	20.2	20.8	20.4
	SD	3.82	2.30	3.38
	Minimum	3	10	3
	Median	21.0	21.0	21.0
	Maximum	24	24	24
Italy	N	15	10	25
	Mean	19.5	20.3	19.8
	SD	3.81	0.48	2.96
	Minimum	6	20	6
	Median	20.0	20.0	20.0
	Maximum	22	21	22
Spain	N	229	116	345
	Mean	18.9	18.8	18.8
	SD	2.24	2.85	2.46
	Minimum	2	2	2
	Median	19.0	19.0	19.0
	Maximum	22	22	22
Pooled countries	N	2646	1348	3994
	Mean	21.8	21.8	21.8
	SD	2.43	2.38	2.41
	Minimum	2	2	2
	Median	22.0	22.0	22.0
	Maximum	28	27	28

Data source = Appendix table IB and IC
N = number of subjects in the considered group or in total (sum of both groups)
Value = value of the considered parameter
SD = standard deviation

Supplement 2 Summary of epidemiological data, by country and for pooled countries – Total vaccinated cohort

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Czech Republic	Number of siblings	0	97	48.7	55	55.0	152	50.8
		1	76	38.2	34	34.0	110	36.8
		2	19	9.5	10	10.0	29	9.7
		3	6	3.0	1	1.0	7	2.3
		6	1	0.5	0	0.0	1	0.3
	Day care at visit 1	No	198	99.5	100	100	298	99.7
		Yes	1	0.5	0	0.0	1	0.3
	Day care at visit 2	No	198	99.5	100	100	298	99.7
		Yes	0	0.0	0	0.0	0	0.0
		Missing	1	0.5	0	0.0	1	0.3
	Day care at visit 3	No	196	98.5	99	99.0	295	98.7
		Yes	2	1.0	1	1.0	3	1.0
		Missing	1	0.5	0	0.0	1	0.3
	Day care at visit 5	No	195	98.0	96	96.0	291	97.3
		Yes	3	1.5	3	3.0	6	2.0
		Missing	1	0.5	1	1.0	2	0.7
	Day care at visit 7	No	194	97.5	96	96.0	290	97.0
		Yes	4	2.0	1	1.0	5	1.7
		Missing	1	0.5	3	3.0	4	1.3
Finland	Number of siblings	0	940	49.0	513	52.8	1453	50.3
		1	596	31.1	283	29.1	879	30.4
		2	260	13.6	121	12.4	381	13.2
		3	92	4.8	35	3.6	127	4.4
		4	21	1.1	13	1.3	34	1.2
		5	5	0.3	4	0.4	9	0.3
		6	2	0.1	0	0.0	2	0.1
		7	2	0.1	2	0.2	4	0.1
		8	0	0.0	1	0.1	1	0.0
	Day care at visit 1	No	1916	99.9	971	99.9	2887	99.9
		Yes	2	0.1	1	0.1	3	0.1
	Day care at visit 2	No	1908	99.5	970	99.8	2878	99.6
		Yes	2	0.1	0	0.0	2	0.1
		Missing	8	0.4	2	0.2	10	0.3
	Day care at visit 3	No	1895	98.8	964	99.2	2859	98.9
		Yes	5	0.3	1	0.1	6	0.2
		Missing	18	0.9	7	0.7	25	0.9
	Day care at visit 5	No	1813	94.5	923	95.0	2736	94.7
		Yes	91	4.7	39	4.0	130	4.5
		Missing	14	0.7	10	1.0	24	0.8
	Day care at visit 6	No	120	6.3	83	8.5	203	7.0
		Yes	30	1.6	11	1.1	41	1.4
		Missing	1768	92.2	878	90.3	2646	91.6
	Day care at visit 7	No	1064	55.5	536	55.1	1600	55.4
		Yes	799	41.7	416	42.8	1215	42.0
		Missing	55	2.9	20	2.1	75	2.6

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
France	Number of siblings	0	30	31.6	13	25.5	43	29.5
		1	48	50.5	28	54.9	76	52.1
		2	10	10.5	6	11.8	16	11.0
		3	5	5.3	2	3.9	7	4.8
		4	1	1.1	0	0.0	1	0.7
		5	1	1.1	1	2.0	2	1.4
		7	0	0.0	1	2.0	1	0.7
	Day care at visit 1	No	94	98.9	47	92.2	141	96.6
		Yes	1	1.1	4	7.8	5	3.4
	Day care at visit 2	No	90	94.7	46	90.2	136	93.2
		Yes	5	5.3	5	9.8	10	6.8
	Day care at visit 3	No	82	86.3	45	88.2	127	87.0
		Yes	11	11.6	5	9.8	16	11.0
		Missing	2	2.1	1	2.0	3	2.1
	Day care at visit 5	No	73	76.8	44	86.3	117	80.1
		Yes	20	21.1	6	11.8	26	17.8
		Missing	2	2.1	1	2.0	3	2.1
	Day care at visit 7	No	62	65.3	37	72.5	99	67.8
		Yes	29	30.5	13	25.5	42	28.8
		Missing	4	4.2	1	2.0	5	3.4
Germany	Number of siblings	0	78	41.1	38	38.4	116	40.1
		1	70	36.8	36	36.4	106	36.7
		2	26	13.7	13	13.1	39	13.5
		3	9	4.7	7	7.1	16	5.5
		4	4	2.1	3	3.0	7	2.4
		5	1	0.5	1	1.0	2	0.7
		6	1	0.5	1	1.0	2	0.7
		7	1	0.5	0	0.0	1	0.3
	Day care at visit 1	No	187	98.4	98	99.0	285	98.6
		Yes	3	1.6	1	1.0	4	1.4
	Day care at visit 2	No	187	98.4	99	100	286	99.0
		Yes	0	0.0	0	0.0	0	0.0
		Missing	3	1.6	0	0.0	3	1.0
	Day care at visit 3	No	178	93.7	96	97.0	274	94.8
		Yes	5	2.6	3	3.0	8	2.8
		Missing	7	3.7	0	0.0	7	2.4
	Day care at visit 5	No	177	93.2	97	98.0	274	94.8
		Yes	2	1.1	0	0.0	2	0.7
		Missing	11	5.8	2	2.0	13	4.5
	Day care at visit 7	No	160	84.2	83	83.8	243	84.1
		Yes	15	7.9	12	12.1	27	9.3
		Missing	15	7.9	4	4.0	19	6.6

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Italy	Number of siblings	0	7	46.7	2	20.0	9	36.0
		1	8	53.3	7	70.0	15	60.0
		2	0	0.0	1	10.0	1	4.0
	Day care at visit 1	No	13	86.7	9	90.0	22	88.0
		Yes	2	13.3	1	10.0	3	12.0
	Day care at visit 2	No	14	93.3	10	100	24	96.0
		Yes	1	6.7	0	0.0	1	4.0
	Day care at visit 3	No	15	100	10	100	25	100
		Yes	0	0.0	0	0.0	0	0.0
	Day care at visit 5	No	13	86.7	10	100	23	92.0
		Yes	1	6.7	0	0.0	1	4.0
		Missing	1	6.7	0	0.0	1	4.0
	Day care at visit 6	No	10	66.7	7	70.0	17	68.0
		Yes	4	26.7	3	30.0	7	28.0
		Missing	1	6.7	0	0.0	1	4.0
	Day care at visit 7	No	9	60.0	6	60.0	15	60.0
		Yes	5	33.3	4	40.0	9	36.0
		Missing	1	6.7	0	0.0	1	4.0
Spain	Number of siblings	0	137	59.8	70	60.3	207	60.0
		1	79	34.5	44	37.9	123	35.7
		2	9	3.9	1	0.9	10	2.9
		3	2	0.9	1	0.9	3	0.9
		4	2	0.9	0	0.0	2	0.6
	Day care at visit 1	No	229	100	115	99.1	344	99.7
		Yes	0	0.0	1	0.9	1	0.3
	Day care at visit 2	No	220	96.1	110	94.8	330	95.7
		Yes	6	2.6	3	2.6	9	2.6
		Missing	3	1.3	3	2.6	6	1.7
	Day care at visit 3	No	217	94.8	107	92.2	324	93.9
		Yes	8	3.5	6	5.2	14	4.1
		Missing	4	1.7	3	2.6	7	2.0
	Day care at visit 4	No	215	93.9	107	92.2	322	93.3
		Yes	10	4.4	6	5.2	16	4.6
		Missing	4	1.7	3	2.6	7	2.0
	Day care at visit 5	No	214	93.4	106	91.4	320	92.8
		Yes	11	4.8	7	6.0	18	5.2
		Missing	4	1.7	3	2.6	7	2.0
	Day care at visit 7	No	147	64.2	72	62.1	219	63.5
		Yes	78	34.1	41	35.3	119	34.5
		Missing	4	1.7	3	2.6	7	2.0

			HRV N = 2646		Placebo N = 1348		Total N = 3994	
Country	**Characteristics**	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Overall total	**Number of siblings**	**0**	1289	48.7	691	51.3	1980	49.6
		1	877	33.1	432	32.0	1309	32.8
		2	324	12.2	152	11.3	476	11.9
		3	114	4.3	46	3.4	160	4.0
		4	28	1.1	16	1.2	44	1.1
		5	7	0.3	6	0.4	13	0.3
		6	4	0.2	1	0.1	5	0.1
		7	3	0.1	3	0.2	6	0.2
		8	0	0.0	1	0.1	1	0.0
	Day care at visit 1	**No**	2637	99.7	1340	99.4	3977	99.6
		Yes	9	0.3	8	0.6	17	0.4
	Day care at visit 2	**No**	2617	98.9	1335	99.0	3952	98.9
		Yes	14	0.5	8	0.6	22	0.6
		Missing	15	0.6	5	0.4	20	0.5
	Day care at visit 3	**No**	2583	97.6	1321	98.0	3904	97.7
		Yes	31	1.2	16	1.2	47	1.2
		Missing	32	1.2	11	0.8	43	1.1
	Day care at visit 5	**No**	2485	93.9	1276	94.7	3761	94.2
		Yes	128	4.8	55	4.1	183	4.6
		Missing	33	1.2	17	1.3	50	1.3
	Day care at visit 7	**No**	1636	61.8	830	61.6	2466	61.7
		Yes	930	35.1	487	36.1	1417	35.5
		Missing	80	3.0	31	2.3	111	2.8

Data source = Appendix table IL

N = number of subjects in the considered group or in total (sum of both groups)

n (%) = number(percentage) of subjects in a given category, by country or for pooled countries

As visit 4 was scheduled for Spain only, 'Day care at visit 4' information has been collected and is presented for that country only.

As visit 6 was optional and performed only if necessary for subjects from Finland and Italy , 'Day care at visit 6' information has been collected only for subjects that came to the visit and is presented for these two countries only.

Supplement 3 Number of days between the second and third dose of routine childhood vaccination – Finland and Italy – ATP cohort for immunogenicity

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Finland	**N**	167	103	270
	Mean	209.5	209.1	209.3
	SD	14.85	15.23	14.97
	Minimum	182	182	182
	Q1	197.0	196.0	197.0
	Median	212.0	213.0	212.0
	Q3	220.0	219.0	220.0
	Maximum	251	245	251
Italy	**N**	12	9	21
	Mean	192.3	199.7	195.5
	SD	22.56	16.22	19.97
	Minimum	155	168	155
	Q1	176.0	189.0	177.0
	Median	189.0	209.0	194.0
	Q3	209.0	209.0	209.0
	Maximum	225	217	225

Data source = Appendix table IC

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the second and the third dose of the routine childhood vaccine(s)

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second and the third dose of the routine childhood vaccine(s)

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Supplement 4 Number of days between the third dose of routine childhood vaccination and the post-vaccination blood sample at visit 5/ 6 – Finland and Italy – ATP cohort for immunogenicity

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Finland	**N**	164	101	265
	Mean	37.5	37.6	37.5
	SD	5.37	4.81	5.15
	Minimum	30	30	30
	Q1	32.0	34.0	33.0
	Median	37.0	38.0	37.0
	Q3	42.5	42.0	42.0
	Maximum	57	48	57
Italy	**N**	12	9	21
	Mean	36.7	37.9	37.2
	SD	5.26	9.56	7.22
	Minimum	32	32	32
	Q1	32.5	33.0	33.0
	Median	35.5	36.0	36.0
	Q3	40.5	36.0	36.0
	Maximum	45	63	63

Data source = Appendix table IC

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the third dose of the routine childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 5/6 available for at least one of the routine childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second and the third dose of the routine childhood vaccine(s)

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Supplement 5 Total number of doses of Infanrix Hexa received from Visit 1 up to 21 days before blood sample 3 at visit 5/6 – Finland – ATP cohort for immunogenicity

	HRV N = 164		Placebo N = 101		Total N = 265	
Parameters or Categories	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
3	164	100	101	100	265	100

Data source = Appendix table IC

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at visit 5/6 for at least one of the Infanrix Hexa antigens available

n (%) = number(percentage) of subjects having received the specified number of doses of the vaccine from the day of visit 1 up to 21 days before the day of blood sampling at visit 5/ 6

Supplement 6 Total number of doses of Infanrix Hexa received from visit 1 up to 21 days before blood sample 3 at visit 5/ 6 – Italy – ATP cohort for immunogenicity

	HRV N = 12		Placebo N = 9		Total N = 21	
Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
3	12	100	9	100	21	100

Data source = Appendix table IC

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at visit 5/6 for at least one of the Infanrix Hexa antigens available

n (%) = number(percentage) of subjects having received the specified number of doses of the vaccine from the day of visit 1 up to 21 days before the day of blood sampling at visit 5/ 6

Supplement 7 Number of days between the second and third dose of routine childhood vaccination – Finland and Italy – Total vaccinated cohort for the reactogenicity and immunogenicity subset

		HRV	Placebo	Total
Country	Statistic	Value	Value	Value
Finland	N	183	110	293
	Mean	209.5	209.6	209.5
	SD	14.85	15.17	14.94
	Minimum	181	182	181
	Q1	197.0	197.0	197.0
	Median	212.0	213.0	212.0
	Q3	220.0	220.0	220.0
	Maximum	251	245	251
Italy	N	14	10	24
	Mean	192.6	195.3	193.8
	SD	21.53	20.61	20.73
	Minimum	155	156	155
	Q1	177.0	187.0	177.0
	Median	189.0	201.5	192.5
	Q3	209.0	209.0	209.0
	Maximum	225	217	225

Data source = Appendix table IC

N= Number of subjects in the considered group or in total (sum of both groups) who have been administered the second and the third dose of the routine childhood vaccine(s)

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second and the third dose of the routine childhood vaccine(s)

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Supplement 8 Number of days between the third dose of routine childhood vaccination and the post-vaccination blood sample at visit 5/ 6 – Finland and Italy – Total vaccinated cohort for the reactogenicity and immunogenicity subset

		HRV	Placebo	Total
Country	**Statistic**	**Value**	**Value**	**Value**
Finland	**N**	175	107	282
	Mean	37.5	37.4	37.5
	SD	5.39	4.86	5.19
	Minimum	30	30	30
	Q1	32.0	33.0	33.0
	Median	37.0	37.0	37.0
	Q3	42.0	42.0	42.0
	Maximum	57	48	57
Italy	**N**	14	10	24
	Mean	36.3	38.6	37.3
	SD	5.00	9.29	7.02
	Minimum	32	32	32
	Q1	32.0	33.0	33.0
	Median	35.5	36.0	36.0
	Q3	36.0	36.0	36.0
	Maximum	45	63	63

Data source = Appendix table IC

N = Number of subjects in the considered group or in total (sum of both groups) who have been administered the third dose of the routine childhood vaccine(s) and with results from the post-vaccination blood sample collected at Visit 5/6 available for at least one of the routine childhood vaccine(s) antigens

Statistics (Mean, SD, Minimum, Q1, Median, Q3, Maximum) are computed on the number of days between the administration of the second and the third dose of the routine childhood vaccine(s)

Q1 = 25th percentile of the distribution of the number of days

Q3 = 75th percentile of the distribution of the number of days

SD = standard deviation of the distribution of the number of days

Supplement 9 Total number of doses of Infanrix Hexa received from visit 1 up to 21 days before blood sample 3 at visit 5/ 6 – Finland – Total vaccinated cohort for the reactogenicity and immunogenicity subset

	HRV N = 175		Placebo N = 107		Total N = 282	
Number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
3	175	100	107	100	282	100

Data source = Appendix table IC

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at visit 5/6 for at least one of the Infanrix Hexa antigens available

n (%) = number (percentage) of subjects having received the specified number of doses of the vaccine from the day of visit 1 up to 21 days before the day of blood sampling at visit 5/ 6

Supplement 10 Total number of doses of Infanrix Hexa received from visit 1 up to 21 days before blood sample 3 at visit 5/ 6 – Italy – Total vaccinated cohort for the reactogenicity and immunogenicity subset

	HRV N = 14		Placebo N = 10		Total N = 24	
Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
3	14	100	10	100	24	100

Data source = Appendix table IC

N = number of subjects in the considered group or in total (sum of both groups) having results from blood sample taken at visit 5/6 for at least one of the Infanrix Hexa antigens available

n (%) = number(percentage) of subjects having received the specified number of doses of the vaccine from the day of visit 1 up to 21 days before the day of blood sampling at visit 5/ 6

Supplement 11 Duration (in years) of the follow-up period from 2 weeks after Dose 2 up Visit 7 - ATP cohort for efficacy

Duration (years) of follow-up period	HRV N= 2572	Placebo N= 1302
Total	3713.9	1886.8
Mean	1.444	1.449
SD	0.137	0.141
Minimum	0.027	0.132
Q1	1.384	1.389
Median	1.458	1.464
Q3	1.526	1.532
Maximum	1.715	1.844

Source: Appendix Table IC

N = number of subjects included in each group

Total= sum of follow-up period expressed in year

SD= standard deviation

Q1= 25th percentile

Q3=75th percentile

Supplement 12 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 7 – ATP cohort for efficacy

	HRV N'= 1569		Placebo N'= 981	
Category	n	%	n	%
No stools collected	142	9.1	102	10.4
Stools collected but no results available*	19	1.2	16	1.6
No stool results available	161	10.3	118	12.0

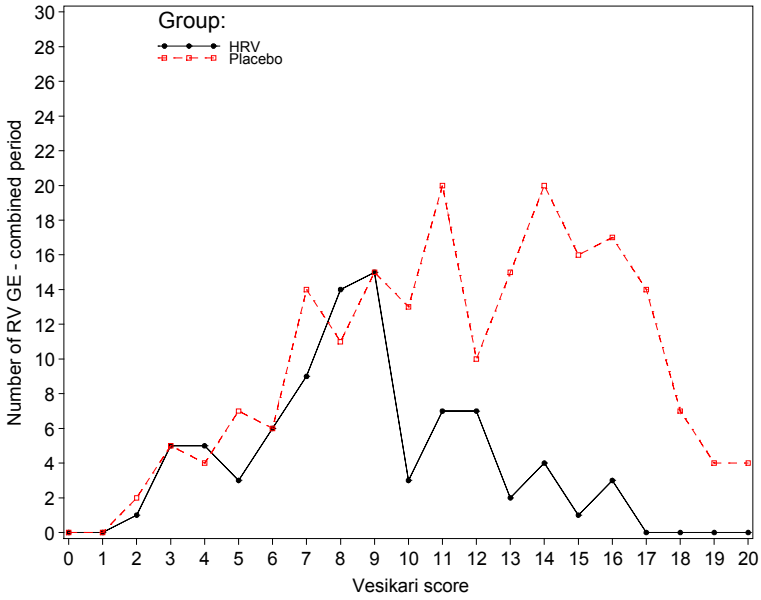
Source: Appendix Table IVB and VA

N'= number of GE episodes reported

n (%)= number(percentage)of GE episodes within the specified category

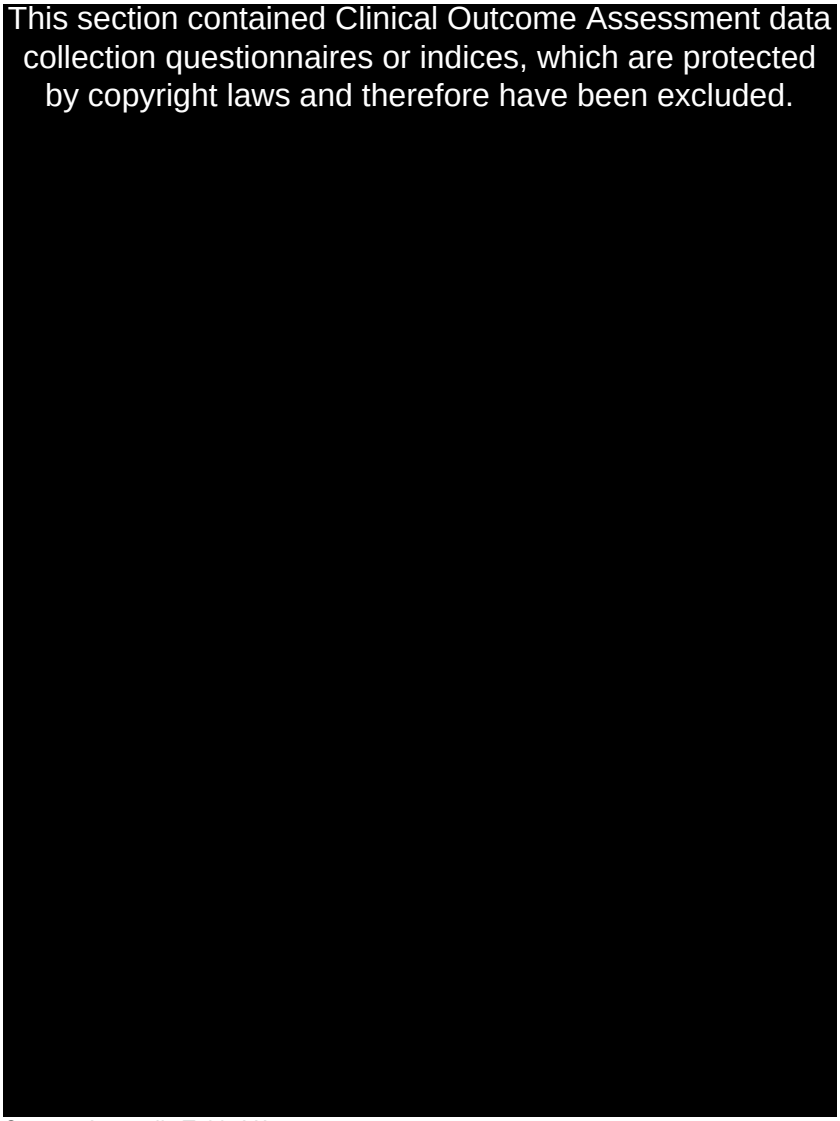
*= due to quantity not sufficient or stool sample not tested

Supplement 13 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7 – ATP cohort for efficacy



Source: Appendix Table IVB and VA

Supplement 14 Characteristics (based on Vesikari scale) of all cause GE episodes reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy



Source: Appendix Table VA
N'= number of all cause 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 Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV N= 2572		Placebo N= 1302	
	n	%	n	%
Any	85	3.3	204	15.7
G1 wild type	18	0.7	89	6.8
G2	14	0.5	17	1.3
G3	3	0.1	10	0.8
G4	6	0.2	18	1.4
G9	38	1.5	71	5.5
GX	1	0.0	1	0.1
P4	16	0.6	16	1.2
P8 wild type	66	2.6	184	14.1
Unknown G type only*	2	0.1	0	0.0
Unknown P type only *	0	0.0	2	0.2
Unknown G and P type*	3	0.1	2	0.2

Source: Appendix Table IVB and VA

N = number of subjects included in each group

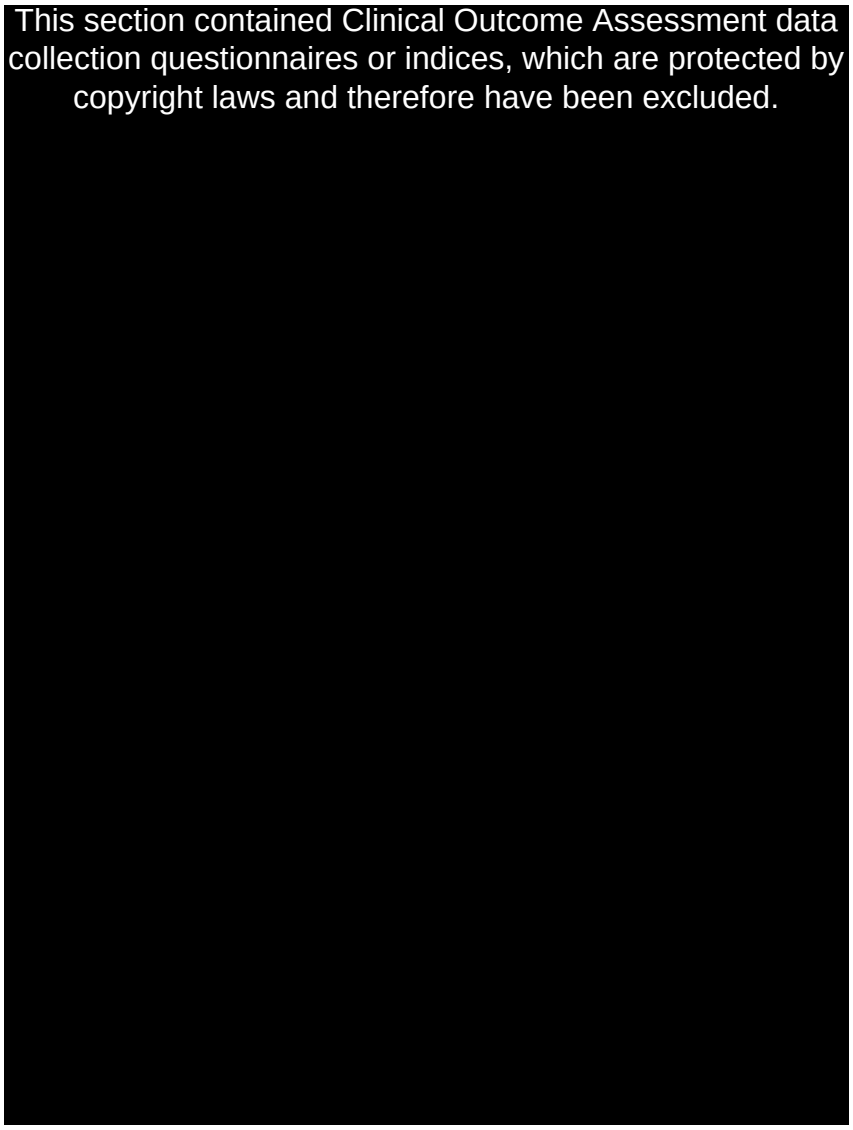
n (%) = number(percentage) of subjects reporting at least once the specified serotype in each group

Any = number of subjects reporting at least one RV GE episode, whatever the serotype

GX = G12

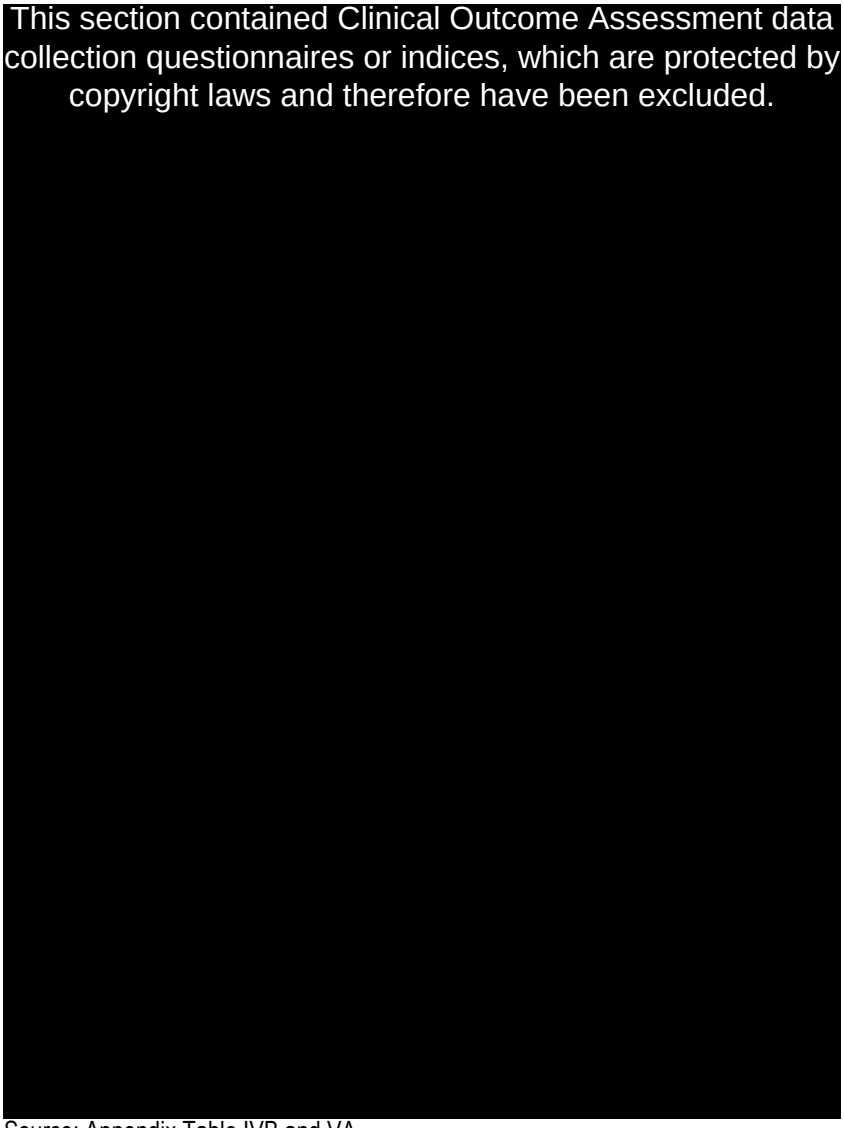
*=not typable

Supplement 16 Characteristics (based on Vesikari scale) of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy



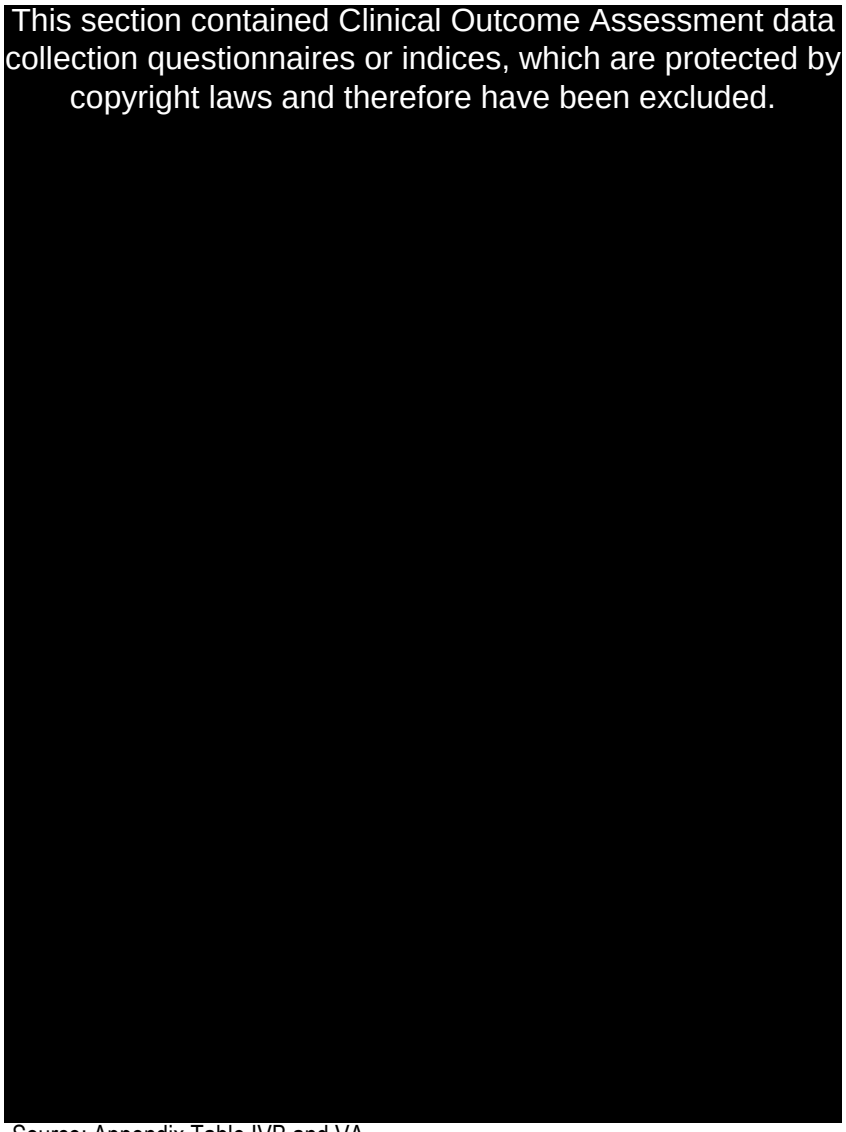
N'= number of RV GE episodes reported in each group
n (%) = number(percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 17 Characteristics (based on Vesikari scale) of RV GE episodes of G1 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy



Source: Appendix Table IVB and VA
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 Characteristics (based on Vesikari scale) of RV GE episodes of G2 + P4 with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy



Source: Appendix Table IVB and VA
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 19 Characteristics (based on Vesikari scale) of RV GE episodes of G3 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

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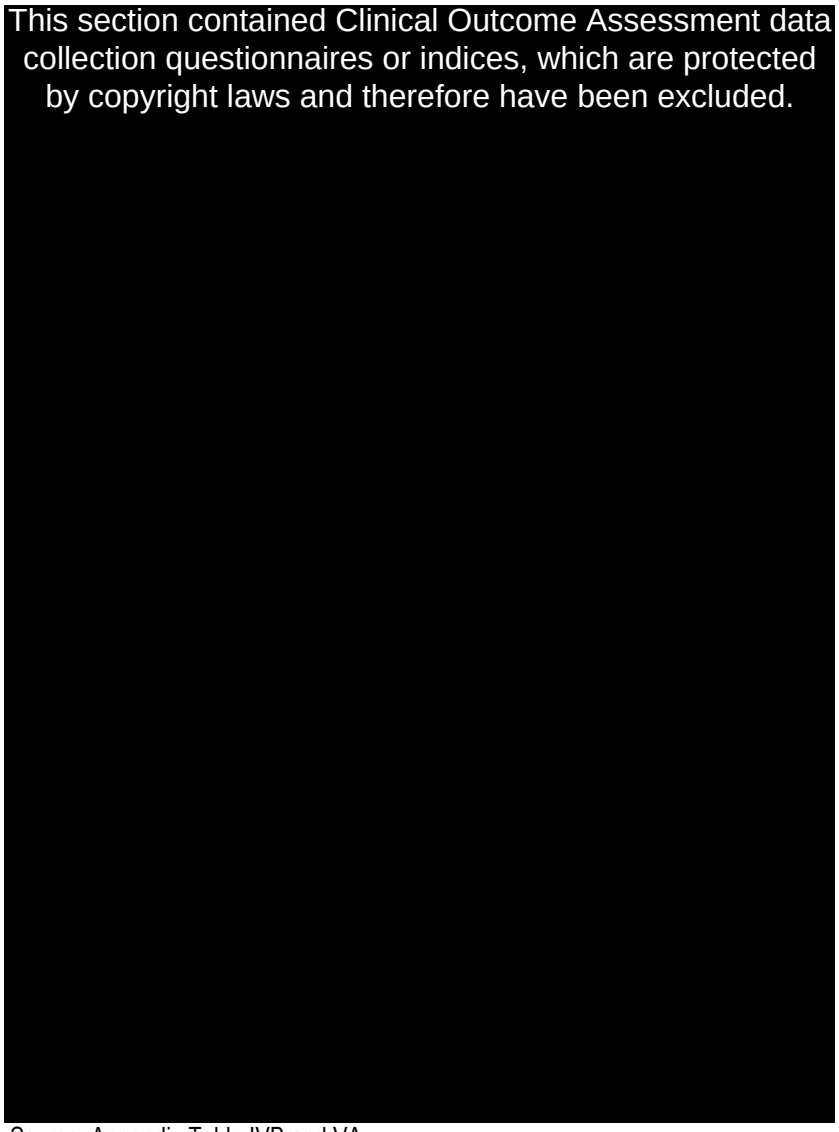
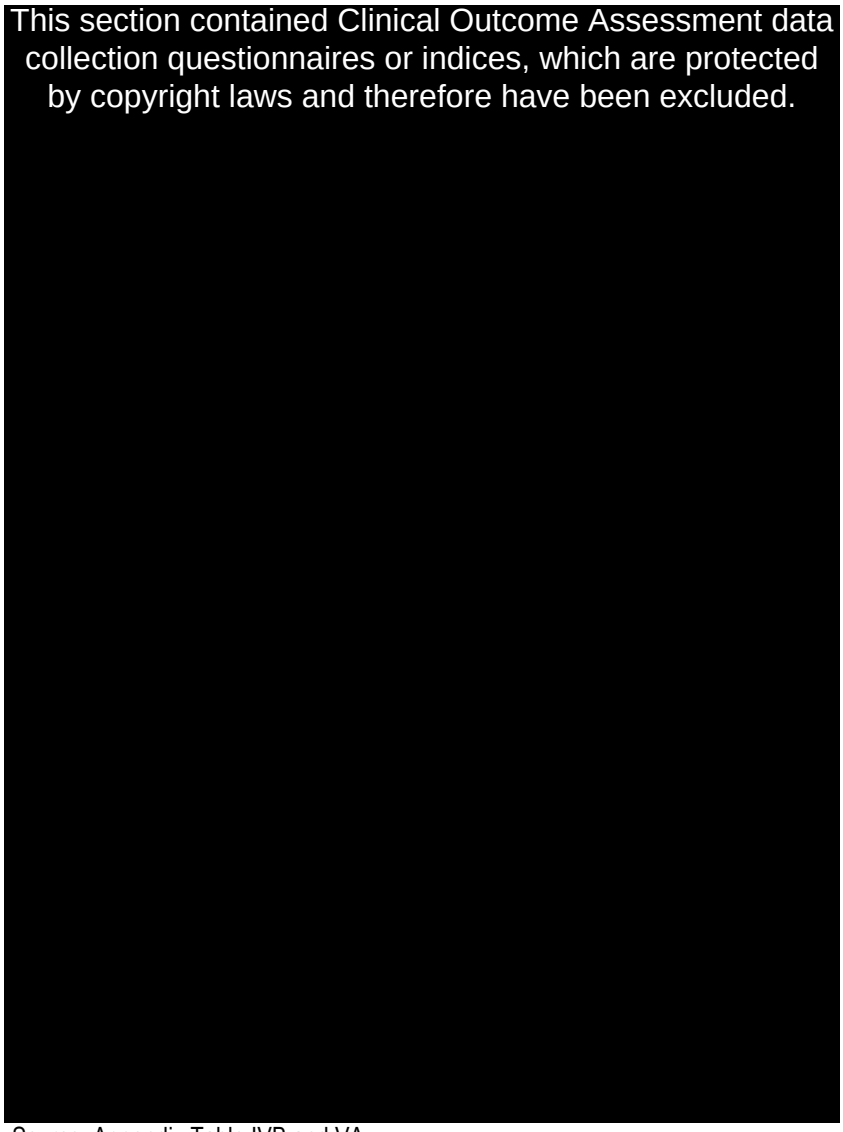
N'= number of RV GE episodes reported in each group
n (%) = number(percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 20 Characteristics (based on Vesikari scale) of RV GE episodes of G4 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy



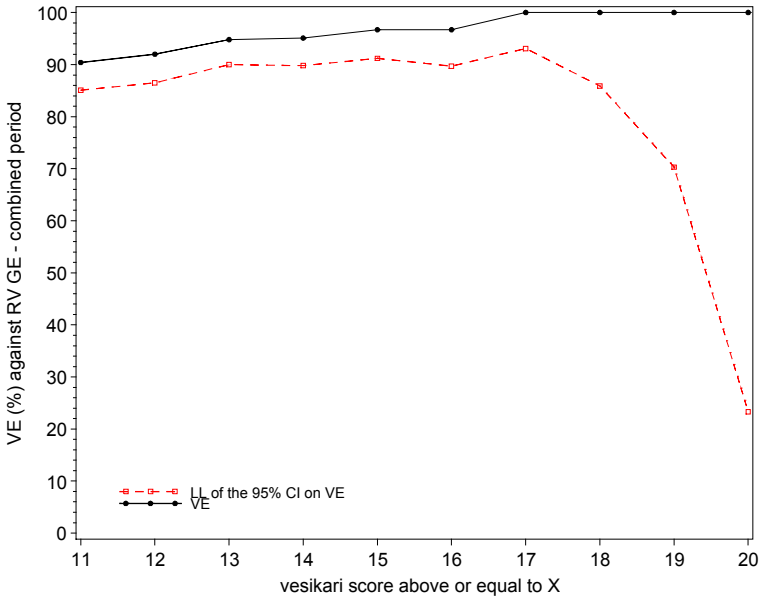
Source: Appendix Table IVB and VA
N'= number of RV GE episodes reported in each group
n (%) = number(percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 21 Characteristics (based on Vesikari scale) of RV GE episodes of G9 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy



Source: Appendix Table IVB and VA
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 22 Vaccine efficacy against RV GE episodes with a score greater than or equal to X on the Vesikari scale from 2 weeks after Dose 2 up to Visit 7 – ATP efficacy cohort



Source: Appendix Table IVB and VA

Supplement 23 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP efficacy cohort

Severity using Vesikari scale	Group	N	n	n/N	95%CI		Vaccine Efficacy	95%CI		P-value
				%	LL	UL	%	LL	UL	
≥11	HRV	2572	24	0.9	0.6	1.4	90.4	85.1	94.1	<0.001
	Placebo	1302	127	9.8	8.2	11.5				
≥12	HRV	2572	17	0.7	0.4	1.1	92.0	86.5	95.5	<0.001
	Placebo	1302	107	8.2	6.8	9.8				
≥13	HRV	2572	10	0.4	0.2	0.7	94.8	90.0	97.6	<0.001
	Placebo	1302	97	7.5	6.1	9.0				
≥14	HRV	2572	8	0.3	0.1	0.6	95.1	89.8	97.9	<0.001
	Placebo	1302	82	6.3	5.0	7.8				
≥15	HRV	2572	4	0.2	0.0	0.4	96.7	91.2	99.1	<0.001
	Placebo	1302	62	4.8	3.7	6.1				
≥16	HRV	2572	3	0.1	0.0	0.3	96.7	89.7	99.3	<0.001
	Placebo	1302	46	3.5	2.6	4.7				
≥17	HRV	2572	0	0.0	0.0	0.1	100.0	93.1	100.0	<0.001
	Placebo	1302	29	2.2	1.5	3.2				
≥18	HRV	2572	0	0.0	0.0	0.1	100.0	85.9	100.0	<0.001
	Placebo	1302	15	1.2	0.6	1.9				
≥19	HRV	2572	0	0.0	0.0	0.1	100.0	70.3	100.0	<0.001
	Placebo	1302	8	0.6	0.3	1.2				
≥20	HRV	2572	0	0.0	0.0	0.1	100.0	23.3	100.0	0.013
	Placebo	1302	4	0.3	0.1	0.8				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Vesikari scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 24 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by status of anti-rotavirus IgA antibodies concentrations at Visit 3 - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 3	Group	N	n	n/N	95%CI		Vaccine Efficacy	95%CI		P-value
				%	LL	UL	%	LL	UL	
Positive	HRV	711	16	2.3	1.3	3.6	65.1	-212.7	91.8	0.171
	Placebo	31	2	6.5	0.8	21.4				
Negative	HRV	110	4	3.6	1.0	9.0	64.9	3.4	90.9	0.025
	Placebo	415	43	10.4	7.6	13.7				
Unknown	HRV	1751	65	3.7	2.9	4.7	80.0	73.2	85.3	<0.001
	Placebo	856	159	18.6	16.0	21.3				

Source: Appendix Table IIIA, IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group, by status of anti-rotavirus IgA antibodies concentrations at Visit 3

95% CI,LL,UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 25 Percentage of subjects reporting severe (Vesikari scale) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by status of anti-rotavirus IgA antibodies concentrations at Visit 3 - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 3	Group	N	n	n/N	95%CI		Vaccine Efficacy	95%CI		P-value
				%	LL	UL	%	LL	UL	
Positive	HRV	711	5	0.7	0.2	1.6	-infinity	-infinity	96.0	1.000
	Placebo	31	0	0.0	0.0	11.2				
Negative	HRV	110	0	0.0	0.0	3.3	100.0	19.2	100.0	0.018
	Placebo	415	19	4.6	2.8	7.1				
Unknown	HRV	1751	19	1.1	0.7	1.7	91.4	85.9	95.0	<0.001
	Placebo	856	108	12.6	10.5	15.0				

Source: Appendix Table IIIA, IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group, by status of anti-rotavirus IgA antibodies concentrations at Visit 3

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 26 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by feeding criteria - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Breast feeding	Group	N	n	%	LL	UL	%	LL	UL	P-value
For at least one dose	HRV	2005	77	3.8	3.0	4.8	76.2	68.7	82.1	<0.001
	Placebo	1041	168	16.1	14.0	18.5				
At none of the doses	HRV	567	8	1.4	0.6	2.8	89.8	77.6	95.9	<0.001
	Placebo	261	36	13.8	9.9	18.6				

Source: Appendix Table IK, IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group, by feeding criteria

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 27 Percentage of subjects reporting severe (Vesikari) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by feeding criteria - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Breast feeding	Group	N	n	%	LL	UL	%	LL	UL	P-value
For at least one dose	HRV	2005	23	1.1	0.7	1.7	88.4	81.6	93.0	<0.001
	Placebo	1041	103	9.9	8.1	11.9				
At none of the doses	HRV	567	1	0.2	0.0	1.0	98.1	88.2	100.0	<0.001
	Placebo	261	24	9.2	6.0	13.4				

Source: Appendix Table IK, IVB and VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group, by feeding criteria

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 28 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by severity using the 24-point Clark scale - ATP cohort for efficacy

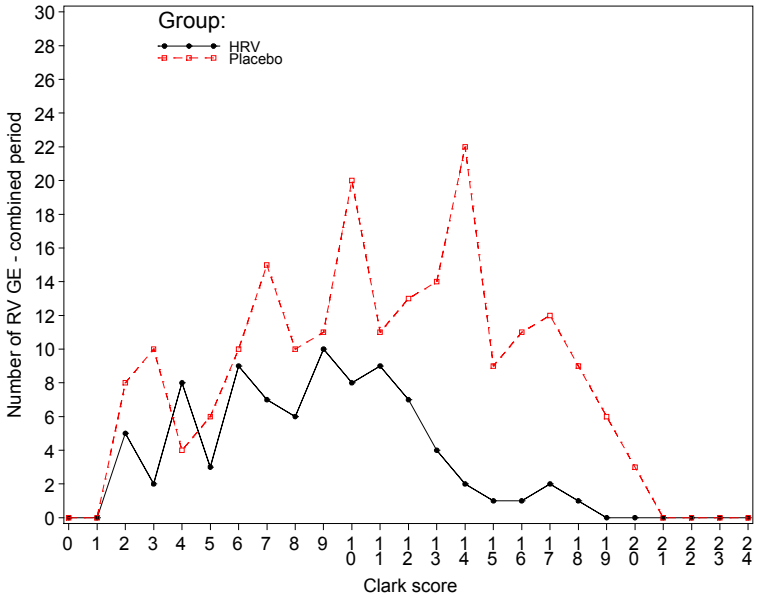
	Severity using	HRV		Placebo	
Event	Clark scale	n	%	n	%
GE	Mild (1-8)	1112	70.9	608	62.0
	Moderate (9-16)	433	27.6	316	32.2
	Severe (≥17)	11	0.7	48	4.9
	Unknown	13	0.8	9	0.9
	Any	1569	100	981	100
RV GE	Mild (1-8)	40	47.1	63	30.9
	Moderate (9-16)	42	49.4	111	54.4
	Severe (≥17)	3	3.5	30	14.7
	Any	85	100	204	100

Source: Appendix Table IVB and VA

n (%) = number (percentage) of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported

Any = any specified symptom reported, regardless of Clark severity scale

Supplement 29 Distribution of Clark score for RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7 – ATP cohort for efficacy



Source: Appendix Table IVB and VA

Supplement 30 Characteristics (based on Clark scale) of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 85 Value or n	HRV N'= 85 %	Placebo N'= 204 Value or n	Placebo N'= 204 %
Severity Score	**Mean**	8.588	-	11.049	-
	SD	3.749	-	4.724	-
	Median	9.0	-	11.0	-
	Minimum	2	-	2	-
	Maximum	18	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	74	87.1	110	53.9
	5-7 days	11	12.9	87	42.6
	> 7 days	0	0.0	7	3.4
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	31	36.5	49	24.0
	5-7	36	42.4	67	32.8
	> 7	18	21.2	88	43.1
Duration of vomiting (days)	**0 - 1 day**	65	76.5	99	48.5
	2 days	15	17.6	50	24.5
	3-5 days	4	4.7	51	25.0
	> 5 days	1	1.2	4	2.0
Maximum number of episodes of Vomiting/24 hours	**0**	36	42.4	43	21.1
	1-3	39	45.9	100	49.0
	4-6	8	9.4	33	16.2
	> 6	2	2.4	28	13.7
Duration of fever (days)	**0 day**	35	41.2	62	30.4
	1-2 day	44	51.8	114	55.9
	3-4 days	6	7.1	26	12.7
	≥ 5 days	0	0.0	2	1.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	35	41.2	62	30.4
	38.0-38.2°C	8	9.4	12	5.9
	38.3-38.7°C	15	17.6	49	24.0
	≥ 38.8°C	27	31.8	81	39.7
Duration of behavioral symptoms	**0 day**	18	21.2	47	23.0
	1-2 days	41	48.2	82	40.2
	3-4 days	23	27.1	54	26.5
	≥ 5 days	3	3.5	21	10.3
Behavioral symptoms	**Behave as usual**	18	21.2	47	23.0
	Irritable/less playful	16	18.8	9	4.4
	Lethargic/listless	50	58.8	143	70.1
	Seizures	1	1.2	5	2.5

Source: Appendix Table IVB and VA

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 Characteristics (based on Clark scale) of RV GE episodes of G1 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 18 Value or n	HRV N'= 18 %	Placebo N'= 85 Value or n	Placebo N'= 85 %
Severity Score	**Mean**	8.444	-	11.424	-
	SD	4.328	-	4.762	-
	Median	7.5	-	11.0	-
	Minimum	2	-	2	-
	Maximum	17	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	14	77.8	43	50.6
	5-7 days	4	22.2	40	47.1
	> 7 days	0	0.0	2	2.4
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	8	44.4	17	20.0
	5-7	7	38.9	29	34.1
	> 7	3	16.7	39	45.9
Duration of vomiting (days)	**0 - 1 day**	14	77.8	40	47.1
	2 days	4	22.2	17	20.0
	3-5 days	0	0.0	25	29.4
	> 5 days	0	0.0	3	3.5
Maximum number of episodes of Vomiting/24 hours	**0**	9	50.0	20	23.5
	1-3	8	44.4	38	44.7
	4-6	1	5.6	15	17.6
	> 6	0	0.0	12	14.1
Duration of fever (days)	**0 day**	8	44.4	25	29.4
	1-2 day	8	44.4	48	56.5
	3-4 days	2	11.1	11	12.9
	≥ 5 days	0	0.0	1	1.2
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	8	44.4	25	29.4
	38.0-38.2°C	4	22.2	5	5.9
	38.3-38.7°C	0	0.0	19	22.4
	≥ 38.8°C	6	33.3	36	42.4
Duration of behavioral symptoms	**0 day**	3	16.7	18	21.2
	1-2 days	5	27.8	31	36.5
	3-4 days	10	55.6	24	28.2
	≥ 5 days	0	0.0	12	14.1
Behavioral symptoms	**Behave as usual**	3	16.7	18	21.2
	Irritable/less playful	4	22.2	5	5.9
	Lethargic/listless	11	61.1	60	70.6
	Seizures	0	0.0	2	2.4

Source: Appendix Table IVB and VA

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 32 Characteristics (based on Clark scale) of RV GE episodes of G2 + P4 with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 14 Value or n	HRV N'= 14 %	Placebo N'= 14 Value or n	Placebo N'= 14 %
Severity Score	**Mean**	8.286	-	8.000	-
	SD	3.604	-	5.505	-
	Median	9.0	-	6.5	-
	Minimum	2	-	2	-
	Maximum	15	-	18	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	13	92.9	10	71.4
	5-7 days	1	7.1	4	28.6
	> 7 days	0	0.0	0	0.0
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	7	50.0	6	42.9
	5-7	5	35.7	4	28.6
	> 7	2	14.3	4	28.6
Duration of vomiting (days)	**0 - 1 day**	11	78.6	8	57.1
	2 days	3	21.4	3	21.4
	3-5 days	0	0.0	3	21.4
	> 5 days	0	0.0	0	0.0
Maximum number of episodes of Vomiting/24 hours	**0**	6	42.9	6	42.9
	1-3	7	50.0	5	35.7
	4-6	1	7.1	2	14.3
	> 6	0	0.0	1	7.1
Duration of fever (days)	**0 day**	6	42.9	9	64.3
	1-2 day	7	50.0	5	35.7
	3-4 days	1	7.1	0	0.0
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	6	42.9	9	64.3
	38.0-38.2°C	0	0.0	0	0.0
	38.3-38.7°C	2	14.3	2	14.3
	≥ 38.8°C	6	42.9	3	21.4
Duration of behavioral symptoms	**0 day**	3	21.4	6	42.9
	1-2 days	8	57.1	5	35.7
	3-4 days	2	14.3	1	7.1
	≥ 5 days	1	7.1	2	14.3
Behavioral symptoms	**Behave as usual**	3	21.4	6	42.9
	Irritable/less playful	2	14.3	1	7.1
	Lethargic/listless	9	64.3	6	42.9
	Seizures	0	0.0	1	7.1

Source: Appendix Table IVB and VA

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 33 Characteristics (based on Clark scale) of RV GE episodes of G3 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 3 Value or n	HRV N'= 3 %	Placebo N'= 10 Value or n	Placebo N'= 10 %
Severity Score	**Mean**	4.333	-	10.700	-
	SD	4.041	-	3.860	-
	Median	2.0	-	11.0	-
	Minimum	2	-	3	-
	Maximum	9	-	16	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	3	100	6	60.0
	5-7 days	0	0.0	3	30.0
	> 7 days	0	0.0	1	10.0
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	2	66.7	3	30.0
	5-7	1	33.3	3	30.0
	> 7	0	0.0	4	40.0
Duration of vomiting (days)	**0 - 1 day**	2	66.7	4	40.0
	2 days	1	33.3	5	50.0
	3-5 days	0	0.0	1	10.0
	> 5 days	0	0.0	0	0.0
Maximum number of episodes of Vomiting/24 hours	**0**	2	66.7	1	10.0
	1-3	1	33.3	5	50.0
	4-6	0	0.0	3	30.0
	> 6	0	0.0	1	10.0
Duration of fever (days)	**0 day**	3	100	4	40.0
	1-2 day	0	0.0	5	50.0
	3-4 days	0	0.0	1	10.0
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	3	100	4	40.0
	38.0-38.2°C	0	0.0	0	0.0
	38.3-38.7°C	0	0.0	0	0.0
	≥ 38.8°C	0	0.0	6	60.0
Duration of behavioral symptoms	**0 day**	2	66.7	2	20.0
	1-2 days	0	0.0	7	70.0
	3-4 days	1	33.3	1	10.0
	≥ 5 days	0	0.0	0	0.0
Behavioral symptoms	**Behave as usual**	2	66.7	2	20.0
	Irritable/less playful	0	0.0	0	0.0
	Lethargic/listless	1	33.3	8	80.0
	Seizures	0	0.0	0	0.0

Source: Appendix Table IVB and VA

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 34 Characteristics (based on Clark scale) of RV GE episodes of G4 + P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 6 Value or n	HRV N'= 6 %	Placebo N'= 17 Value or n	Placebo N'= 17 %
Severity Score	**Mean**	8.833	-	11.471	-
	SD	3.189	-	4.460	-
	Median	9.0	-	11.0	-
	Minimum	5	-	2	-
	Maximum	14	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	6	100	8	47.1
	5-7 days	0	0.0	9	52.9
	> 7 days	0	0.0	0	0.0
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	2	33.3	5	29.4
	5-7	3	50.0	6	35.3
	> 7	1	16.7	6	35.3
Duration of vomiting (days)	**0 - 1 day**	5	83.3	9	52.9
	2 days	0	0.0	3	17.6
	3-5 days	1	16.7	4	23.5
	> 5 days	0	0.0	1	5.9
Maximum number of episodes of Vomiting/24 hours	**0**	2	33.3	3	17.6
	1-3	4	66.7	10	58.8
	4-6	0	0.0	2	11.8
	> 6	0	0.0	2	11.8
Duration of fever (days)	**0 day**	2	33.3	5	29.4
	1-2 day	3	50.0	10	58.8
	3-4 days	1	16.7	2	11.8
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	2	33.3	5	29.4
	38.0-38.2°C	0	0.0	0	0.0
	38.3-38.7°C	3	50.0	3	17.6
	≥ 38.8°C	1	16.7	9	52.9
Duration of behavioral symptoms	**0 day**	0	0.0	2	11.8
	1-2 days	4	66.7	8	47.1
	3-4 days	2	33.3	6	35.3
	≥ 5 days	0	0.0	1	5.9
Behavioral symptoms	**Behave as usual**	0	0.0	2	11.8
	Irritable/less playful	4	66.7	0	0.0
	Lethargic/listless	2	33.3	15	88.2
	Seizures	0	0.0	0	0.0

Source: Appendix Table IVB and VA

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 35 Characteristics (based on Clark scale) of RV GE episodes of G9 +P8 wild type with no other G type reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 38 Value or n	HRV N'= 38 %	Placebo N'= 69 Value or n	Placebo N'= 69 %
Severity Score	**Mean**	9.079	-	11.377	-
	SD	3.752	-	4.637	-
	Median	9.5	-	12.0	-
	Minimum	2	-	2	-
	Maximum	18	-	19	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	33	86.8	36	52.2
	5-7 days	5	13.2	29	42.0
	> 7 days	0	0.0	4	5.8
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	10	26.3	15	21.7
	5-7	17	44.7	23	33.3
	> 7	11	28.9	31	44.9
Duration of vomiting (days)	**0 - 1 day**	30	78.9	32	46.4
	2 days	5	13.2	20	29.0
	3-5 days	2	5.3	17	24.6
	> 5 days	1	2.6	0	0.0
Maximum number of episodes of Vomiting/24 hours	**0**	16	42.1	10	14.5
	1-3	15	39.5	38	55.1
	4-6	6	15.8	11	15.9
	> 6	1	2.6	10	14.5
Duration of fever (days)	**0 day**	12	31.6	15	21.7
	1-2 day	24	63.2	42	60.9
	3-4 days	2	5.3	11	15.9
	≥ 5 days	0	0.0	1	1.4
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	12	31.6	15	21.7
	38.0-38.2°C	4	10.5	7	10.1
	38.3-38.7°C	9	23.7	24	34.8
	≥ 38.8°C	13	34.2	23	33.3
Duration of behavioral symptoms	**0 day**	9	23.7	16	23.2
	1-2 days	20	52.6	27	39.1
	3-4 days	7	18.4	20	29.0
	≥ 5 days	2	5.3	6	8.7
Behavioral symptoms	**Behave as usual**	9	23.7	16	23.2
	Irritable/less playful	5	13.2	3	4.3
	Lethargic/listless	23	60.5	48	69.6
	Seizures	1	2.6	2	2.9

Source: Appendix Table IVB and VA

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 36 Characteristics (based on Clark scale) of all cause GE episodes reported from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV N'= 1569 Value or n	HRV N'= 1569 %	Placebo N'= 981 Value or n	Placebo N'= 981 %
Severity Score	**Mean**	6.405	-	7.608	-
	SD	3.736	-	4.558	-
	Median	6.0	-	7.0	-
	Minimum	0	-	0	-
	Maximum	20	-	23	-
Duration of looser than normal stools (days)	**0 day**	14	0.9	10	1.0
	1-4 days	1105	70.4	654	66.7
	5-7 days	329	21.0	248	25.3
	> 7 days	121	7.7	69	7.0
Maximum number of looser than normal stools/24 hours	**0**	14	0.9	10	1.0
	2-4	631	40.2	337	34.4
	5-7	652	41.6	398	40.6
	> 7	272	17.3	236	24.1
Duration of vomiting (days)	**0 - 1 day**	1357	86.5	735	74.9
	2 days	125	8.0	124	12.6
	3-5 days	77	4.9	112	11.4
	> 5 days	10	0.6	10	1.0
Maximum number of episodes of Vomiting/24 hours	**0**	1014	64.6	541	55.1
	1-3	431	27.5	296	30.2
	4-6	95	6.1	88	9.0
	> 6	29	1.8	56	5.7
Duration of fever (days)	**0 day**	1106	70.5	591	60.2
	1-2 day	371	23.6	316	32.2
	3-4 days	74	4.7	65	6.6
	≥ 5 days	18	1.1	9	0.9
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	1106	70.5	591	60.2
	38.0-38.2°C	96	6.1	64	6.5
	38.3-38.7°C	120	7.6	123	12.5
	≥ 38.8°C	247	15.7	203	20.7
Duration of behavioral symptoms	**0 day**	779	49.6	418	42.6
	1-2 days	522	33.3	346	35.3
	3-4 days	193	12.3	152	15.5
	≥ 5 days	75	4.8	65	6.6
Behavioral symptoms	**Behave as usual**	779	49.6	418	42.6
	Irritable/less playful	231	14.7	132	13.5
	Lethargic/listless	535	34.1	415	42.3
	Seizures	24	1.5	16	1.6

Source: Appendix Table VA

N'= number of all cause 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 37 Percentage of subjects reporting severe (Clark score greater than 16 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2572	3	0.1	0.0	0.3	94.9	83.7	99.0	<0.001
Placebo	1302	30	2.3	1.6	3.3				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 38 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Clark scale and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7 - ATP efficacy cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Severity using Clark scale	Group	N	n	%	LL	UL	%	LL	UL	P-value
≥17	HRV	2572	3	0.1	0.0	0.3	94.9	83.7	99.0	<0.001
	Placebo	1302	30	2.3	1.6	3.3				
≥18	HRV	2572	1	0.0	0.0	0.2	97.2	82.2	99.9	<0.001
	Placebo	1302	18	1.4	0.8	2.2				
≥19	HRV	2572	0	0.0	0.0	0.1	100.0	74.4	100.0	<0.001
	Placebo	1302	9	0.7	0.3	1.3				
≥20	HRV	2572	0	0.0	0.0	0.1	100.0	-22.5	100.0	0.038
	Placebo	1302	3	0.2	0.0	0.7				
≥21	HRV	2572	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1302	0	0.0	0.0	0.3				
≥22	HRV	2572	0	0.0	0.0	0.1	-	-	-	
	Placebo	1302	0	0.0	0.0	0.3				
≥23	HRV	2572	0	0.0	0.0	0.1	-	-	-	
	Placebo	1302	0	0.0	0.0	0.3				
≥24	HRV	2572	0	0.0	0.0	0.1	-	-	-	
	Placebo	1302	0	0.0	0.0	0.3				

Source: Appendix Table IVB and VA

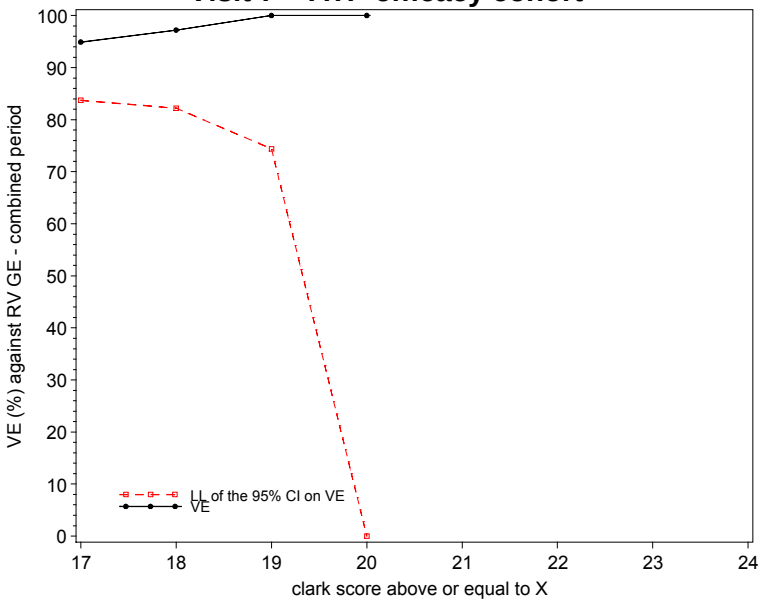
N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Clark scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 39 Vaccine efficacy against RV GE episodes with a score greater than or equal to X on the Clark scale from 2 weeks after Dose 2 up to Visit 7 – ATP efficacy cohort



Source: Appendix Table IVB and VA
Y-axis has been cut at 0

Supplement 40 Percentage of subjects reporting severe (Clark score greater than 16 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2572	1	0.0	0.0	0.2	96.4	76.2	99.9	<0.001
Placebo	1302	14	1.1	0.6	1.8				
G2									
HRV	2572	0	0.0	0.0	0.1	100.0	-1874.3	100.0	0.336
Placebo	1302	1	0.1	0.0	0.4				
G3									
HRV	2572	0	0.0	0.0	0.1	-	-	-	-
Placebo	1302	0	0.0	0.0	0.3				
G4									
HRV	2572	0	0.0	0.0	0.1	100.0	-169.5	100.0	0.113
Placebo	1302	2	0.2	0.0	0.6				
G9									
HRV	2572	2	0.1	0.0	0.3	92.2	65.6	99.1	<0.001
Placebo	1302	13	1.0	0.5	1.7				
Pooled Non G1 (G2, G4, G9)									
HRV	2572	2	0.1	0.0	0.3	93.7	73.1	99.3	<0.001
Placebo	1302	16	1.2	0.7	2.0	-	-	-	-

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 41 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G serotype and P genotype and by country - ATP cohort for efficacy

Country	Serotype	HRV N' = 85		Placebo N' = 204	
		n	%	N	%
Czech Republic	G1WT+P8WT	0	0.0	4	66.7
	G2+P4	1	33.3	1	16.7
	G4+P8WT	1	33.3	0	0.0
	G9+P8WT	0	0.0	1	16.7
	GX+P8WT	1	33.3	0	0.0
Finland	G1WT+G4+P8WT	0	0.0	1	0.6
	G1WT+G9+P8WT	0	0.0	1	0.6
	G1WT and unknown P type*	0	0.0	1	0.6
	G1WT+G2+P4	0	0.0	1	0.6
	G1WT+P8WT	15	21.7	79	43.9
	G2 and unknown P type*	0	0.0	1	0.6
	G2+G9+P4	0	0.0	1	0.6
	G2+P4	12	17.4	12	6.7
	G3+P8WT	2	2.9	10	5.6
	G4+P8WT	4	5.8	16	8.9
	G9+P8WT	32	46.4	54	30.0
	GX+P8WT	0	0.0	1	0.6
	P4 and unknown G type*	1	1.4	0	0.0
	Unknown G and P type*	3	4.3	2	1.1
France	G1WT+P8WT	1	33.3	2	33.3
	G9+P8WT	2	66.7	4	66.7
Germany	G1WT+P8WT	1	33.3	0	0.0
	G2+P4	1	33.3	1	100
	G4+P8WT	1	33.3	0	0.0
Spain	G1WT+P8WT	1	14.3	0	0.0
	G3+P8WT	1	14.3	0	0.0
	G4+P8WT	0	0.0	1	9.1
	G9+P8WT	4	57.1	10	90.9
	P4 and unknown G type*	1	14.3	0	0.0

Source: Appendix Table IVB and VA
N'= number of RV GE episodes reported
n (%)= number(percentage) of RV GE episodes reported in each group, by G serotype and P genotype
wt = wild type
GX = G12
* = not typable

Supplement 42 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	193	3	1.6	0.3	4.5	74.9	-17.7	95.9	0.065
	Placebo	97	6	6.2	2.3	13.0				
Finland	**HRV**	1893	69	3.6	2.8	4.6	80.6	74.3	85.6	<0.001
	Placebo	956	180	18.8	16.4	21.5				
France	**HRV**	95	3	3.2	0.7	9.0	73.7	-23.2	95.7	0.064
	Placebo	50	6	12.0	4.5	24.3				
Germany	**HRV**	179	3	1.7	0.3	4.8	-57.5	-8170.5	87.4	1.000
	Placebo	94	1	1.1	0.0	5.8	-	-	-	-
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	7	3.6	1.4	7.2	69.3	13.3	89.9	0.016
	Placebo	95	11	11.6	5.9	19.8	-	-	-	-

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI,LL,UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 43 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	193	0	0.0	0.0	1.9	100.0	-167.6	100.0	0.111
	Placebo	97	2	2.1	0.3	7.3				
Finland	HRV	1893	21	1.1	0.7	1.7	90.9	85.4	94.5	<0.001
	Placebo	956	116	12.1	10.1	14.4				
France	HRV	95	1	1.1	0.0	5.7	82.5	-118.5	99.7	0.118
	Placebo	50	3	6.0	1.3	16.5				
Germany	HRV	179	0	0.0	0.0	2.0	-	-	-	-
	Placebo	94	0	0.0	0.0	3.8				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	197	2	1.0	0.1	3.6	83.9	10.1	98.4	0.016
	Placebo	95	6	6.3	2.4	13.2				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 44 Percentage of subjects reporting any RV GE episodes requiring medical attention and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	193	3	1.6	0.3	4.5	74.9	-17.7	95.9	0.065
	Placebo	97	6	6.2	2.3	13.0				
Finland	HRV	1893	25	1.3	0.9	1.9	88.1	81.4	92.6	<0.001
	Placebo	956	106	11.1	9.2	13.3				
France	HRV	95	3	3.2	0.7	9.0	68.4	-62.3	95.1	0.125
	Placebo	50	5	10.0	3.3	21.8				
Germany	HRV	179	3	1.7	0.3	4.8	-57.5	-8170.5	87.4	1.000
	Placebo	94	1	1.1	0.0	5.8				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	197	7	3.6	1.4	7.2	66.2	1.8	89.1	0.029
	Placebo	95	10	10.5	5.2	18.5				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV requiring medical attention in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 45 Percentage of subjects reporting all cause GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by country - ATP cohort for efficacy

Country	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Czech Republic	**HRV**	193	76	39.4	32.4	46.7	6.8	-39.7	37.1	0.704
	Placebo	97	41	42.3	32.3	52.7				
Finland	**HRV**	1893	856	45.2	43.0	47.5	15.2	5.2	24.1	<0.001
	Placebo	956	510	53.3	50.1	56.5				
France	**HRV**	95	36	37.9	28.1	48.4	29.8	-20.2	58.6	0.078
	Placebo	50	27	54.0	39.3	68.2				
Germany	**HRV**	179	31	17.3	12.1	23.7	9.6	-71.7	51.0	0.741
	Placebo	94	18	19.1	11.8	28.6				
Italy	**HRV**	15	4	26.7	7.8	55.1	-infinity	-infinity	56.0	0.125
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	93	47.2	40.1	54.4	12.1	-26.3	38.2	0.319
	Placebo	95	51	53.7	43.2	64.0				

Source: Appendix Table VA

N = number of subjects included in each group

n (%) = number(percentage) of subjects reporting at least one GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 46 Percentage of subjects reporting all cause severe (Vesikari scale) GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by country - ATP cohort for efficacy

Country	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Czech Republic	**HRV**	193	19	9.8	6.0	14.9	-19.4	-215.2	50.1	0.831
	Placebo	97	8	8.2	3.6	15.6				
Finland	**HRV**	1893	202	10.7	9.3	12.1	52.8	42.5	61.2	<0.001
	Placebo	956	216	22.6	20.0	25.4				
France	**HRV**	95	5	5.3	1.7	11.9	67.1	-14.0	91.5	0.062
	Placebo	50	8	16.0	7.2	29.1				
Germany	**HRV**	179	3	1.7	0.3	4.8	68.5	-61.9	95.1	0.129
	Placebo	94	5	5.3	1.7	12.0				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	27	13.7	9.2	19.3	34.9	-22.4	64.8	0.127
	Placebo	95	20	21.1	13.4	30.6				

Source: Appendix Table VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 47 Percentage of subjects reporting severe (Clark score greater than 16 points) RV GE episodes and vaccine efficacy from 2 weeks after Dose 2 up to Visit 7, by country - ATP cohort for efficacy

Country	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Czech Republic	**HRV**	193	0	0.0	0.0	1.9	-	-	-	-
	Placebo	97	0	0.0	0.0	3.7				
Finland	**HRV**	1893	3	0.2	0.0	0.5	94.2	81.0	98.9	<0.001
	Placebo	956	26	2.7	1.8	4.0				
France	**HRV**	95	0	0.0	0.0	3.8	100.0	-1952.6	100.0	0.345
	Placebo	50	1	2.0	0.1	10.6				
Germany	**HRV**	179	0	0.0	0.0	2.0	-	-	-	-
	Placebo	94	0	0.0	0.0	3.8				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	0	0.0	0.0	1.9	100.0	-16.7	100.0	0.034
	Placebo	95	3	3.2	0.7	9.0				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 48 Percentage of subjects who reported GE episodes and RV GE episodes during the second efficacy period - ATP cohort for efficacy

Event	Total number of episode reported	HRV N = 2554 n	HRV N = 2554 %	Placebo N = 1294 n	Placebo N = 1294 %
GE	**1**	573	22.4	315	24.3
	2	124	4.9	96	7.4
	3	25	1.0	13	1.0
	4	5	0.2	3	0.2
	5	1	0.0	2	0.2
	Any	728	28.5	429	33.2
RV GE	**1**	61	2.4	110	8.5
	Any	61	2.4	110	8.5

Source: Appendix Table IVB and VA

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 episode

Supplement 49 Percentage of GE episodes with no available stool results during the second efficacy period – ATP cohort for efficacy

Category	HRV N'= 921		Placebo N'= 568	
	n	%	n	%
No stools collected	100	10.9	68	12.0
Stools collected but no results available*	7	0.8	6	1.1
No stool results available	107	11.6	74	13.0

Source: Appendix Table IVB and VA
N'= number of GE episodes reported
n (%)= number(percentage) of GE episodes within the specified category
*= due to quantity not sufficient or stool sample not tested

Supplement 50 Number of GE episodes and RV GE episodes reported during the second efficacy period, by severity using the 20-point Vesikari scale - ATP cohort for efficacy

Event	Severity using Vesikari scale	HRV		Placebo	
		n	%	n	%
GE	**Mild (1-6)**	431	46.8	209	36.8
	Moderate (7-10)	324	35.2	195	34.3
	Severe (≥11)	158	17.2	159	28.0
	Unknown	8	0.9	5	0.9
	Any	921	100	568	100
RV GE	**Mild (1-6)**	12	19.7	13	11.8
	Moderate (7-10)	30	49.2	30	27.3
	Severe (≥11)	19	31.1	67	60.9
	Any	61	100	110	100

Source: Appendix Table IVB and VA
n (%) = number(percentage) of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported
Any = any specified symptom reported, regardless of Vesikari severity scale

Supplement 51 Number of GE episodes and RV GE episodes reported during the second efficacy period, by severity using the 24-point Clark scale - ATP cohort for efficacy

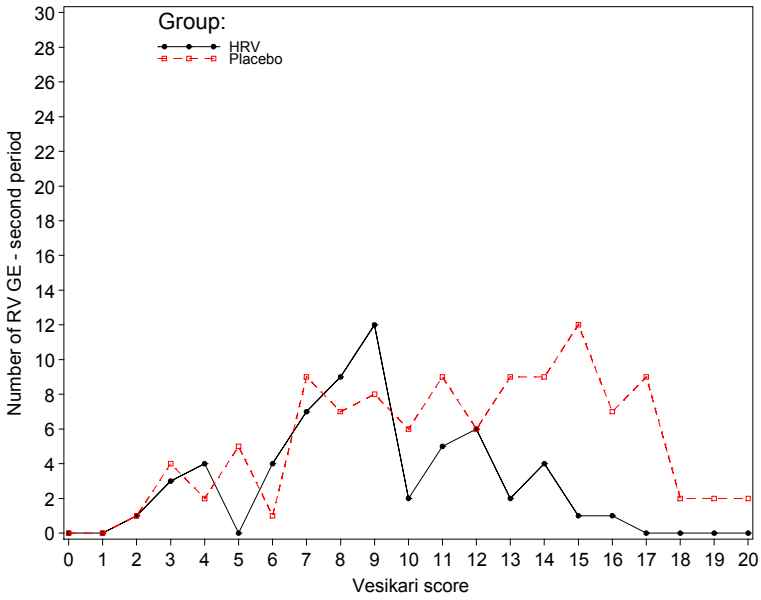
Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	Mild (1-8)	650	70.6	356	62.7
	Moderate (9-16)	255	27.7	177	31.2
	Severe (≥17)	6	0.7	27	4.8
	Unknown	10	1.1	8	1.4
	Any	921	100	568	100
RV GE	Mild (1-8)	28	45.9	35	31.8
	Moderate (9-16)	32	52.5	60	54.5
	Severe (≥17)	1	1.6	15	13.6
	Any	61	100	110	100

Source: Appendix Table IVB and VA

n (%) = number (percentage) of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported

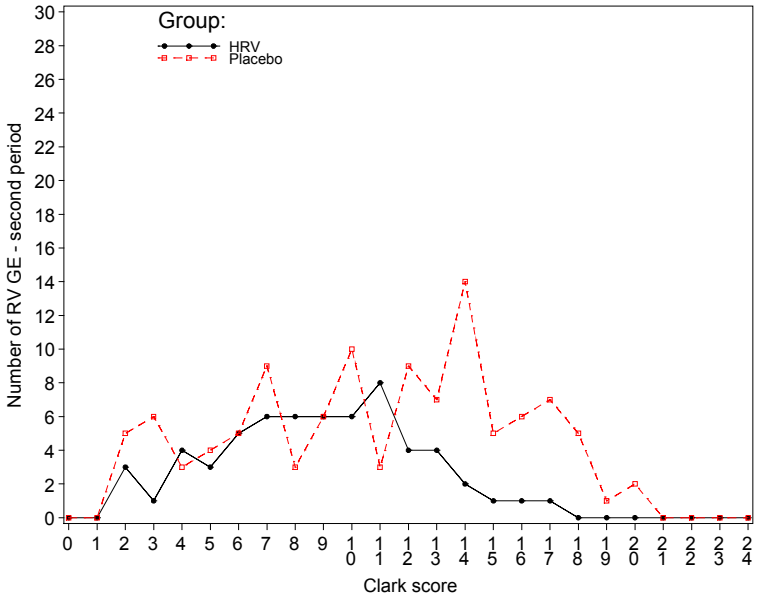
Any = any specified symptom reported, regardless of Clark severity scale

Supplement 52 Distribution of Vesikari score for RV GE episodes reported during the second efficacy period – ATP cohort for efficacy



Source: Appendix Table IVB and VA

Supplement 53 Distribution of Clark score for RV GE episodes reported during the second efficacy period – ATP cohort for efficacy



Source: Appendix Table IVB and VA

Supplement 54 Percentage of subjects with RV GE episodes reported during the second efficacy period, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV N= 2554		Placebo N= 1294	
	n	%	n	%
Any	61	2.4	110	8.5
G1 wild type	14	0.5	43	3.3
G2	11	0.4	13	1.0
G3	2	0.1	5	0.4
G4	3	0.1	5	0.4
G9	25	1.0	44	3.4
GX	1	0.0	1	0.1
P4	13	0.5	13	1.0
P8 wild type	45	1.8	94	7.3
Unknown G type only*	2	0.1	0	0.0
Unknown P type only *	0	0.0	1	0.1
Unknown G and P type*	3	0.1	2	0.2

Source: Appendix Table IVB and VA
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
GX = G12
* = not typable

Supplement 55 Number of RV GE episodes reported during the second efficacy period, by G serotype and P genotype - ATP cohort for efficacy

		HRV N' = 61		Placebo N' = 110	
Country	**Serotype**	**n**	**%**	**N**	**%**
Czech Republic	**G1WT+P8WT**	0	0.0	1	50.0
	G2+P4	0	0.0	1	50.0
	GX+P8WT	1	100	0	0.0
Finland	**G1WT+G9+P8WT**	0	0.0	1	1.0
	G1WT and unknown P type*	0	0.0	1	1.0
	G1WT+G2+P4	0	0.0	1	1.0
	G1WT+P8WT	12	24.0	38	39.6
	G2+G9+P4	0	0.0	1	1.0
	G2+P4	10	20.0	9	9.4
	G3+P8WT	1	2.0	5	5.2
	G4+P8WT	3	6.0	5	5.2
	G9+P8WT	20	40.0	32	33.3
	GX+P8WT	0	0.0	1	1.0
	P4 and unknown G type*	1	2.0	0	0.0
	Unknown G and P type*	3	6.0	2	2.1
France	**G1WT+P8WT**	0	0.0	1	100
	G9+P8WT	1	100	0	0.0
Germany	**G1WT+P8WT**	1	50.0	0	0.0
	G2+P4	1	50.0	1	100
Spain	**G1WT+P8WT**	1	14.3	0	0.0
	G3+P8WT	1	14.3	0	0.0
	G9+P8WT	4	57.1	10	100
	P4 and unknown G type*	1	14.3	0	0.0
All countries	**G1WT+G9+P8WT**	0	0.0	1	0.9
	G1WT and unknown P type*	0	0.0	1	0.9
	G1WT+G2+P4	0	0.0	1	0.9
	G1WT+P8WT	14	23.0	40	36.4
	G2+G9+P4	0	0.0	1	0.9
	G2+P4	11	18.0	11	10.0
	G3+P8WT	2	3.3	5	4.5
	G4+P8WT	3	4.9	5	4.5
	G9+P8WT	25	41.0	42	38.2
	GX+P8WT	1	1.6	1	0.9
	P4 and unknown G type*	2	3.3	0	0.0
	Unknown G and P type*	3	4.9	2	1.8

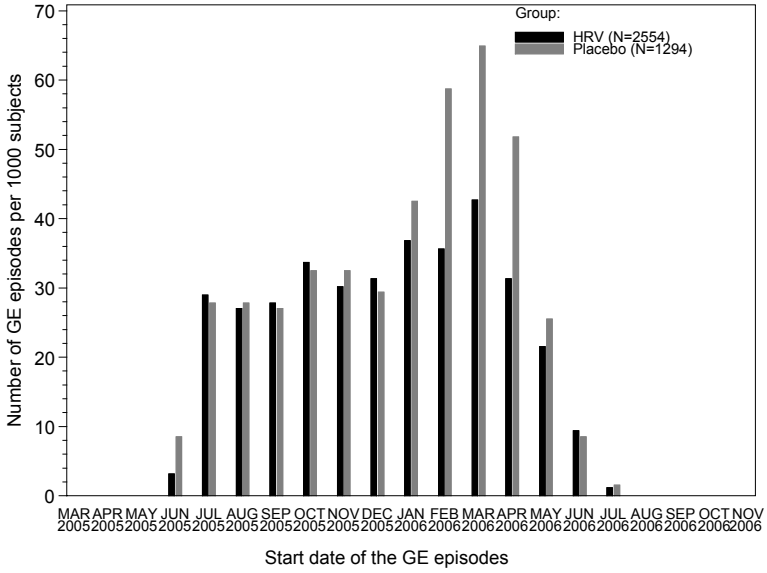
Source: Appendix Table IVB and VA
N'= number of RV GE episodes reported
n (%)= number (percentage) of RV GE episodes reported in each group, by G serotype and P genotype
GX = G12
wt=wild type
*=not typable

Supplement 56 Duration (in years) of the follow-up period during the second efficacy period - ATP cohort for efficacy

Duration (years) of follow-up period	HRV N= 2554	Placebo N= 1294
Total	2497.2	1266.0
Mean	0.978	0.978
SD	0.064	0.072
Minimum	0.047	0.077
Q1	0.942	0.942
Median	0.981	0.981
Q3	1.011	1.014
Maximum	1.268	1.364

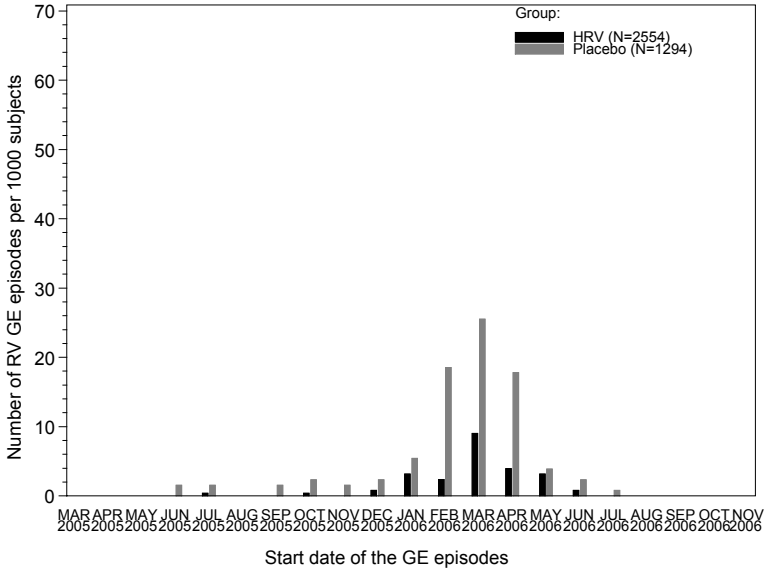
Source: Appendix Table IC
N = number of subjects included in each group
Total= sum of follow-up period expressed in year
SD= standard deviation
Q1= 25th percentile
Q3=75th percentile

Supplement 57 Seasonal distribution of GE episodes reported during the second efficacy period – All countries – ATP efficacy cohort



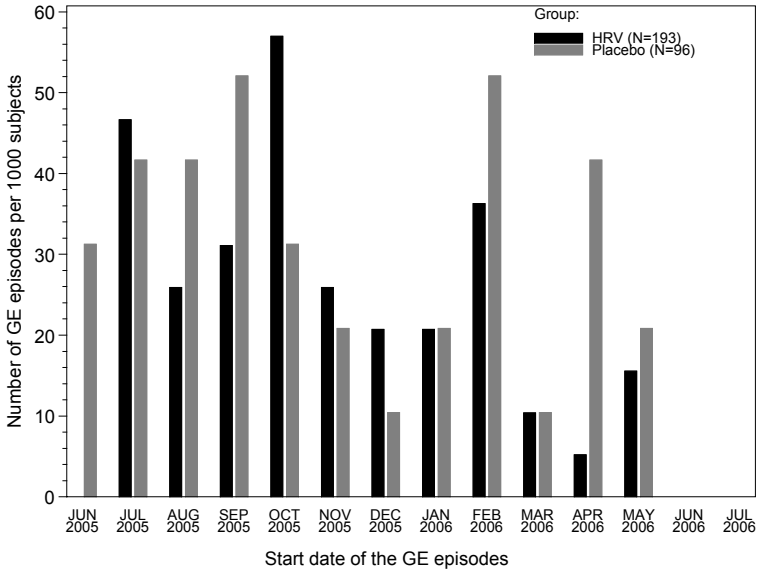
Source: Appendix Table VA
N = number of subjects included in each group

Supplement 58 Seasonal distribution of RV GE episodes reported during the second efficacy period – All countries – ATP efficacy cohort



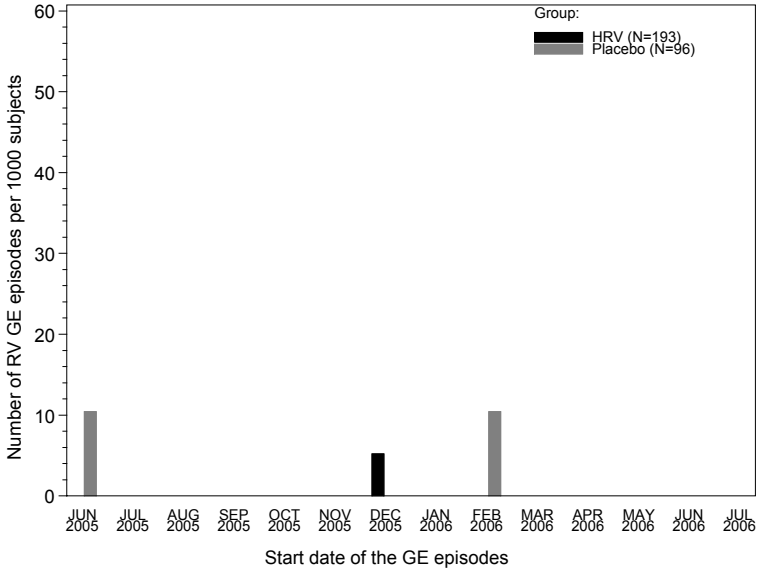
Source: Appendix Table IVB and VA
N = number of subjects included in each group

Supplement 59 Seasonal distribution of GE episodes reported during the second efficacy period – Czech Republic – ATP efficacy cohort



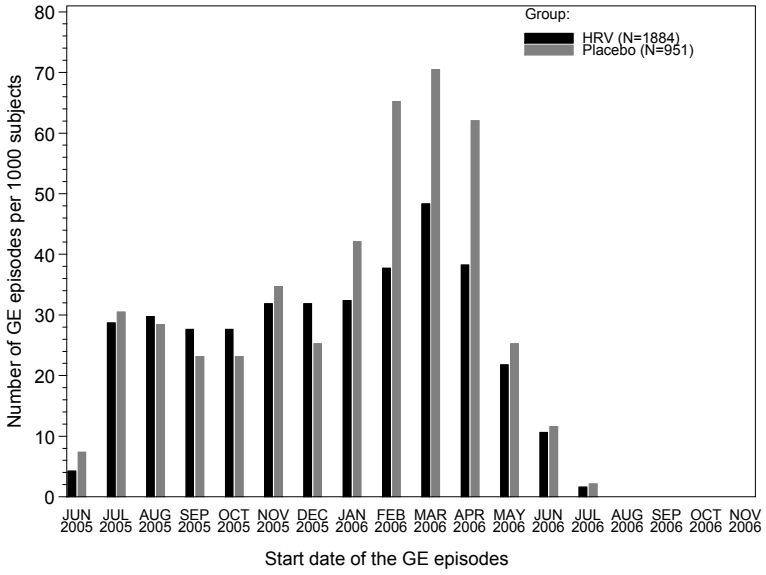
Source: Appendix Table VA
N = number of subjects included in each group

Supplement 60 Seasonal distribution of RV GE episodes reported during the second efficacy period – Czech Republic – ATP efficacy cohort



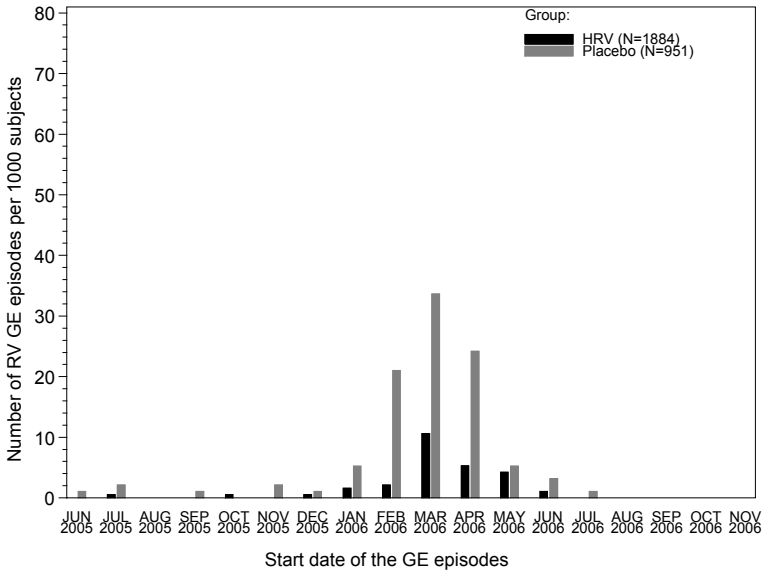
Source: Appendix Table IVB and VA
N = number of subjects included in each group

Supplement 61 Seasonal distribution of GE episodes reported during the second efficacy period – Finland – ATP efficacy cohort



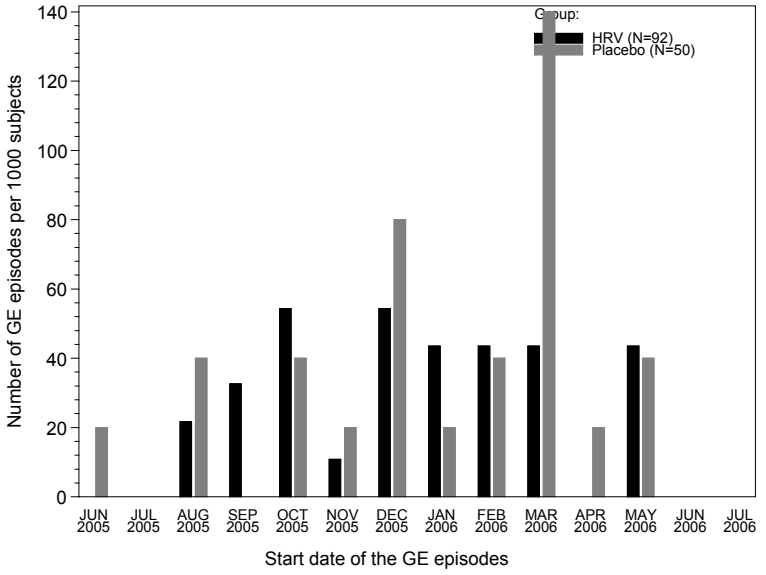
Source: Appendix Table VA
N = number of subjects included in each group

Supplement 62 Seasonal distribution of RV GE episodes reported during the second efficacy period – Finland – ATP efficacy cohort



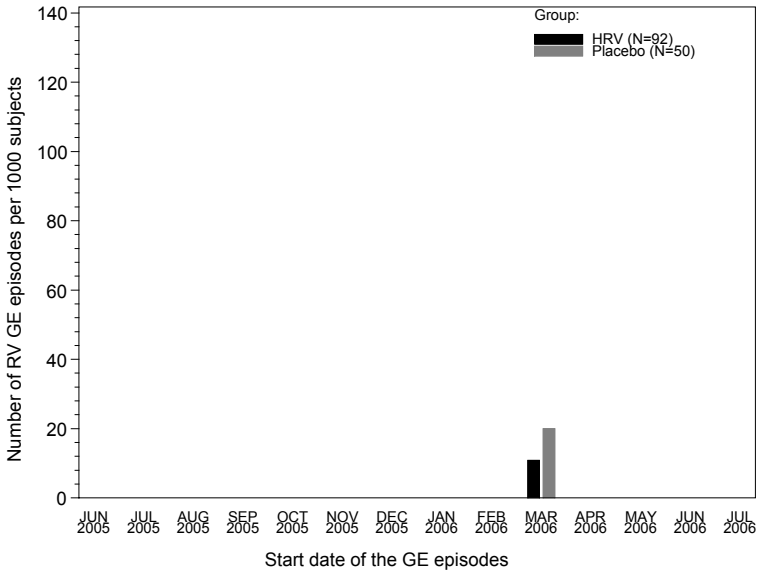
Source: Appendix Table IVB and VA
N = number of subjects included in each group

Supplement 63 Seasonal distribution of GE episodes reported during the second efficacy period – France – ATP efficacy cohort



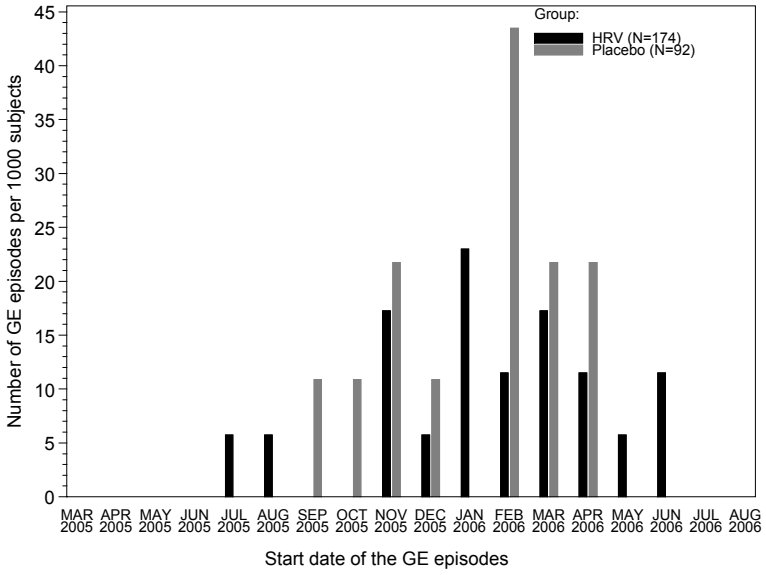
Source: Appendix Table VA
N = number of subjects included in each group

Supplement 64 Seasonal distribution of RV GE episodes reported during the second efficacy period – France – ATP efficacy cohort



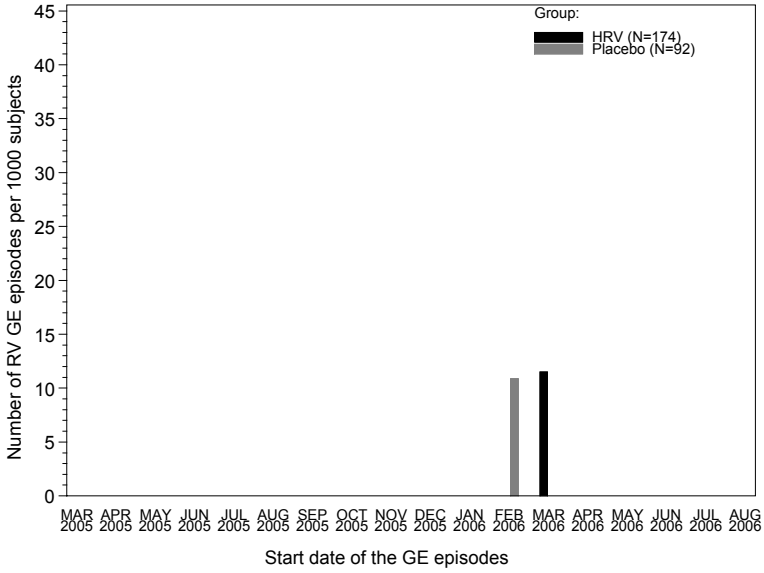
Source: Appendix Table IVB and VA
N = number of subjects included in each group

Supplement 65 Seasonal distribution of GE episodes reported during the second efficacy period – Germany – ATP efficacy cohort



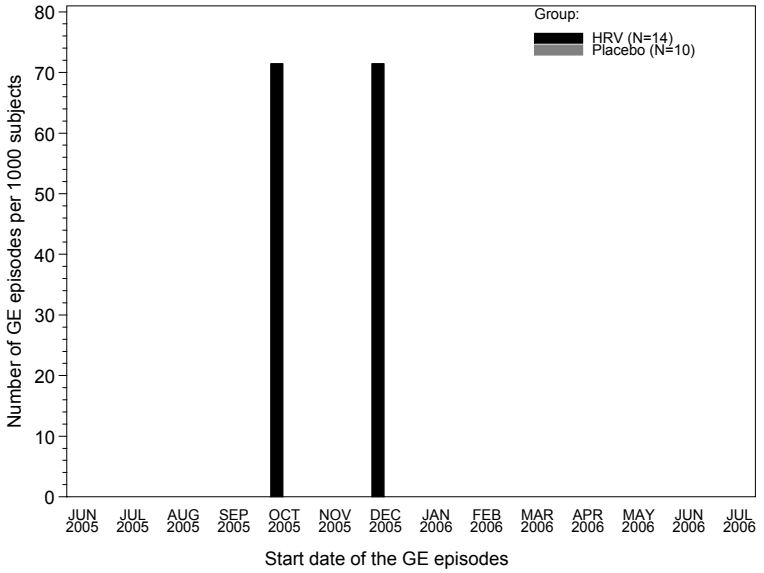
Source: Appendix Table VA
N = number of subjects included in each group

Supplement 66 Seasonal distribution of RV GE episodes reported during the second efficacy period – Germany – ATP efficacy cohort



Source: Appendix Table IVB and VA
N = number of subjects included in each group

Supplement 67 Seasonal distribution of GE episodes reported during the second efficacy period – Italy – ATP efficacy cohort

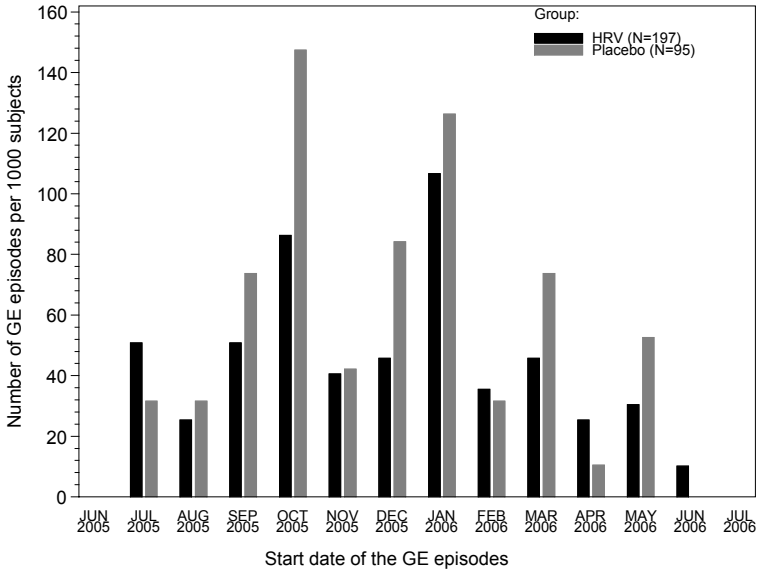


Source: Appendix Table VA
N = number of subjects included in each group

Supplement 68 Seasonal distribution of RV GE episodes reported during the second efficacy period – Italy – ATP efficacy cohort

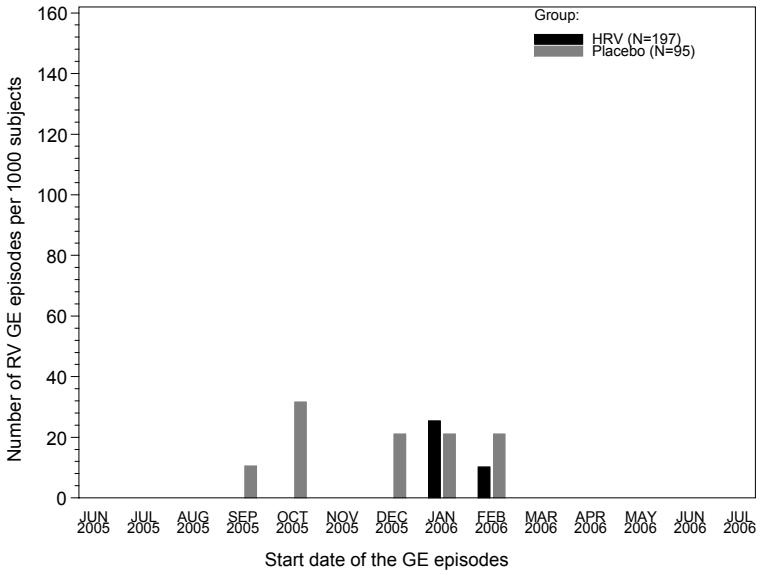
No RV GE episodes reported in Italy

Supplement 69 Seasonal distribution of GE episodes reported during the second efficacy period – Spain – ATP efficacy cohort



Source: Appendix Table VA
N = number of subjects included in each group

Supplement 70 Seasonal distribution of RV GE episodes during the second efficacy period – Spain – ATP efficacy cohort



Source: Appendix Table IVB and VA
N = number of subjects included in each group

Supplement 71 Percentage of subjects reporting any RV GE episodes and vaccine efficacy during the second efficacy period - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2554	61	2.4	1.8	3.1	71.9	61.2	79.8	<0.001
Placebo	1294	110	8.5	7.0	10.2				

Source: Appendix Table IVB and VA
N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 72 Percentage of subjects reporting any RV GE episodes and vaccine efficacy during the second efficacy period, by country - ATP cohort for efficacy

Country	Group	N	n	n/N %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Czech Republic	**HRV**	193	1	0.5	0.0	2.9	75.1	-377.7	99.6	0.257
	Placebo	96	2	2.1	0.3	7.3				
Finland	**HRV**	1884	50	2.7	2.0	3.5	73.7	62.6	81.7	<0.001
	Placebo	951	96	10.1	8.3	12.2				
France	**HRV**	92	1	1.1	0.0	5.9	45.7	-4166.1	99.3	1.000
	Placebo	50	1	2.0	0.1	10.6				
Germany	**HRV**	174	2	1.1	0.1	4.1	-5.7	-6138.8	94.5	1.000
	Placebo	92	1	1.1	0.0	5.9				
Italy	**HRV**	14	0	0.0	0.0	23.2	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	7	3.6	1.4	7.2	66.2	1.8	89.1	0.029
	Placebo	95	10	10.5	5.2	18.5				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 73 Percentage of subjects reporting any RV GE episodes and vaccine efficacy during the second efficacy period, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2554	14	0.5	0.3	0.9	83.5	69.3	91.7	<0.001
Placebo	1294	43	3.3	2.4	4.5				
G2									
HRV	2554	11	0.4	0.2	0.8	57.1	-3.7	82.6	0.048
Placebo	1294	13	1.0	0.5	1.7				
G3									
HRV	2554	2	0.1	0.0	0.3	79.7	-23.8	98.1	0.047
Placebo	1294	5	0.4	0.1	0.9				
G4									
HRV	2554	3	0.1	0.0	0.3	69.6	-56.2	95.3	0.128
Placebo	1294	5	0.4	0.1	0.9				
G9									
HRV	2554	25	1.0	0.6	1.4	71.2	51.9	83.1	<0.001
Placebo	1294	44	3.4	2.5	4.5				
Pooled Non G1 (G2, G3, G4, G9, GX)									
HRV	2554	42	1.6	1.2	2.2	68.2	52.6	78.9	<0.001
Placebo	1294	67	5.2	4.0	6.5				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified RV GE episode in each group

GX = G12

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 74 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11 points) RV GE episodes and vaccine efficacy during the second efficacy period - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2554	19	0.7	0.4	1.2	85.6	75.8	91.9	<0.001
Placebo	1294	67	5.2	4.0	6.5				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 75 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11 points) RV GE episodes and vaccine efficacy during the second efficacy period, by country - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	193	0	0.0	0.0	1.9	-	-	-	-
	Placebo	96	0	0.0	0.0	3.8				
Finland	**HRV**	1884	17	0.9	0.5	1.4	85.7	75.2	92.2	<0.001
	Placebo	951	60	6.3	4.8	8.0				
France	**HRV**	92	0	0.0	0.0	3.9	100.0	-2019.6	100.0	0.352
	Placebo	50	1	2.0	0.1	10.6				
Germany	**HRV**	174	0	0.0	0.0	2.1	-	-	-	-
	Placebo	92	0	0.0	0.0	3.9				
Italy	**HRV**	14	0	0.0	0.0	23.2	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	2	1.0	0.1	3.6	83.9	10.1	98.4	0.016
	Placebo	95	6	6.3	2.4	13.2				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 76 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11 points) RV GE episodes and vaccine efficacy during the second efficacy period, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2554	2	0.1	0.0	0.3	96.5	86.2	99.6	<0.001
Placebo	1294	29	2.2	1.5	3.2	-	-	-	-
G2									
HRV	2554	1	0.0	0.0	0.2	89.9	9.4	99.8	0.018
Placebo	1294	5	0.4	0.1	0.9				
G3									
HRV	2554	1	0.0	0.0	0.2	83.1	-110.3	99.7	0.114
Placebo	1294	3	0.2	0.0	0.7				
G4									
HRV	2554	1	0.0	0.0	0.2	87.3	-28.0	99.7	0.047
Placebo	1294	4	0.3	0.1	0.8				
G9									
HRV	2554	11	0.4	0.2	0.8	77.7	53.0	90.1	<0.001
Placebo	1294	25	1.9	1.3	2.8				
Pooled Non G1 (G2, G3, G4, G9, GX)									
HRV	2554	14	0.5	0.3	0.9	80.8	63.7	90.4	<0.001
Placebo	1294	37	2.9	2.0	3.9				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified severe RV GE episode in each group

GX = G12

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 77 Percentage of subjects reporting severe (Clark score greater than 16 points) RV GE episodes and vaccine efficacy during the second efficacy period - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2554	1	0.0	0.0	0.2	96.6	78.0	99.9	<0.001
Placebo	1294	15	1.2	0.7	1.9				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 78 Percentage of subjects reporting severe (Clark score greater than 16 points) RV GE episodes and vaccine efficacy during the second efficacy period, by country - ATP cohort for efficacy

Country	Group	N	n	n/N %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Czech Republic	**HRV**	193	0	0.0	0.0	1.9	-	-	-	-
	Placebo	96	0	0.0	0.0	3.8				
Finland	**HRV**	1884	1	0.1	0.0	0.3	95.8	71.6	99.9	<0.001
	Placebo	951	12	1.3	0.7	2.2				
France	**HRV**	92	0	0.0	0.0	3.9	-	-	-	-
	Placebo	50	0	0.0	0.0	7.1				
Germany	**HRV**	174	0	0.0	0.0	2.1	-	-	-	-
	Placebo	92	0	0.0	0.0	3.9				
Italy	**HRV**	14	0	0.0	0.0	23.2	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	0	0.0	0.0	1.9	100.0	-16.7	100.0	0.034
	Placebo	95	3	3.2	0.7	9.0				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 79 Percentage of subjects reporting severe (Clark score greater than 16 points) RV GE episodes and vaccine efficacy during the second efficacy period, by RV serotype - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2554	0	0.0	0.0	0.1	100.0	57.0	100.0	0.001
Placebo	1294	6	0.5	0.2	1.0				
G2									
HRV	2554	0	0.0	0.0	0.1	100.0	-1876.0	100.0	0.336
Placebo	1294	1	0.1	0.0	0.4				
G3									
HRV	2554	0	0.0	0.0	0.1	-	-	-	-
Placebo	1294	0	0.0	0.0	0.3				
G4									
HRV	2554	0	0.0	0.0	0.1	100.0	-1876.0	100.0	0.336
Placebo	1294	1	0.1	0.0	0.4				
G9									
HRV	2554	1	0.0	0.0	0.2	92.8	43.7	99.8	0.003
Placebo	1294	7	0.5	0.2	1.1				
Pooled Non G1 (G2, G4, G9)									
HRV	2554	1	0.0	0.0	0.2	94.4	59.4	99.9	<0.001
Placebo	1294	9	0.7	0.3	1.3				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 80 Percentage of subjects reporting all cause GE episodes and vaccine efficacy during the second efficacy period, by country and for all countries - ATP cohort for efficacy

Country	Group	N	n	n/N %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Czech Republic	**HRV**	193	44	22.8	17.1	29.4	18.9	-36.1	50.9	0.384
	Placebo	96	27	28.1	19.4	38.2				
Finland	**HRV**	1884	557	29.6	27.5	31.7	14.0	1.1	25.1	0.010
	Placebo	951	327	34.4	31.4	37.5				
France	**HRV**	92	25	27.2	18.4	37.4	28.5	-37.4	62.2	0.190
	Placebo	50	19	38.0	24.7	52.8				
Germany	**HRV**	174	18	10.3	6.2	15.9	4.8	-130.8	58.3	1.000
	Placebo	92	10	10.9	5.3	19.1				
Italy	**HRV**	14	2	14.3	1.8	42.8	-infinity	-infinity	86.6	0.493
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	82	41.6	34.7	48.8	14.0	-26.2	40.8	0.314
	Placebo	95	46	48.4	38.0	58.9				
All countries	**HRV**	2554	728	28.5	26.8	30.3	14.0	2.9	23.8	0.003
	Placebo	1294	429	33.2	30.6	35.8				

Source: Appendix Table VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 81 Percentage of subjects reporting all cause severe (Vesikari scale) GE episodes and vaccine efficacy during the second efficacy period, by country - ATP cohort for efficacy

Country	Group	N	n	n/N %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Czech Republic	**HRV**	193	10	5.2	2.5	9.3	-24.4	-443.2	64.1	1.000
	Placebo	96	4	4.2	1.1	10.3				
Finland	**HRV**	1884	112	5.9	4.9	7.1	53.7	39.6	64.5	<0.001
	Placebo	951	122	12.8	10.8	15.1				
France	**HRV**	92	3	3.3	0.7	9.2	67.4	-67.6	94.9	0.130
	Placebo	50	5	10.0	3.3	21.8				
Germany	**HRV**	174	2	1.1	0.1	4.1	73.6	-84.5	97.6	0.186
	Placebo	92	4	4.3	1.2	10.8				
Italy	**HRV**	14	0	0.0	0.0	23.2	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	22	11.2	7.1	16.4	41.1	-16.6	69.8	0.101
	Placebo	95	18	18.9	11.6	28.3				
All countries	**HRV**	2554	149	5.8	5.0	6.8	50.7	37.8	60.9	<0.001
	Placebo	1294	153	11.8	10.1	13.7				

Source: Appendix Table VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 82 Percentage of subjects hospitalized due to RV GE episodes and vaccine efficacy during the second efficacy period - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2554	2	0.1	0.0	0.3	92.2	65.6	99.1	<0.001
Placebo	1294	13	1.0	0.5	1.7				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects hospitalized due to RV GE episode caused by the circulating wild-type RV

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 83 Percentage of subjects hospitalized due to GE episodes and vaccine efficacy during the second efficacy period - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2554	18	0.7	0.4	1.1	64.9	33.5	81.9	<0.001
Placebo	1294	26	2.0	1.3	2.9				

Source: Appendix Table VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects hospitalized due to GE episode

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 84 Percentage of subjects reporting any RV GE episodes requiring medical attention and vaccine efficacy during the second efficacy period, by country and for all countries - ATP cohort for efficacy

Country	Group	N	n	n/N %	n/N 95%CI LL	n/N 95%CI UL	Vaccine Efficacy %	Vaccine Efficacy 95%CI LL	Vaccine Efficacy 95%CI UL	P-value
Czech Republic	**HRV**	193	1	0.5	0.0	2.9	75.1	-377.7	99.6	0.257
	Placebo	96	2	2.1	0.3	7.3				
Finland	**HRV**	1884	20	1.1	0.6	1.6	81.0	67.6	89.2	<0.001
	Placebo	951	53	5.6	4.2	7.2				
France	**HRV**	92	1	1.1	0.0	5.9	45.7	-4166.1	99.3	1.000
	Placebo	50	1	2.0	0.1	10.6				
Germany	**HRV**	174	2	1.1	0.1	4.1	-5.7	-6138.8	94.5	1.000
	Placebo	92	1	1.1	0.0	5.9				
Italy	**HRV**	14	0	0.0	0.0	23.2	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	197	7	3.6	1.4	7.2	62.5	-13.2	88.1	0.053
	Placebo	95	9	9.5	4.4	17.2				
All countries	**HRV**	2554	31	1.2	0.8	1.7	76.2	63.0	85.0	<0.001
	Placebo	1294	66	5.1	4.0	6.4				

Source: Appendix Table IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV requiring medical attention in each group

95% CI,LL,UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 85 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 up to Visit 7 – Total vaccinated cohort

Group	N	n	n/N %	n/N 95%CI LL	n/N 95%CI UL
HRV	2646	5*	0.2	0.1	0.4
Placebo	1348	0	0.0	0.0	0.3

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects with vaccine virus in at least one stool sample collected in case of GE episode

95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit

*four episodes of G1/P8 vaccine strain and one episode of G1/P8 vaccine strain with G9/P8 wild type

Supplement 86 Percentage of subjects who reported GE episodes and RV GE episodes from Dose 1 up to Visit 7 - Total vaccinated cohort

Event	Total number of episode reported	HRV N= 2646 n	HRV N= 2646 %	Placebo N= 1348 n	Placebo N= 1348 %
GE	1	788	29.8	432	32.0
	2	292	11.0	196	14.5
	3	97	3.7	63	4.7
	4	31	1.2	16	1.2
	5	6	0.2	7	0.5
	6	5	0.2	1	0.1
	7	0	0.0	1	0.1
	Any	1219	46.1	716	53.1
RV GE	1	87	3.3	215	15.9
	Any	87	3.3	215	15.9

Source: Appendix Table IIB, IIC, IVB and VA
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 episode

Supplement 87 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 7 - Total vaccinated cohort

Category	HRV N'= 1847 n	HRV N'= 1847 %	Placebo N'= 1125 n	Placebo N'= 1125 %
No stools collected	174	9.4	117	10.4
Stools collected but no results available*	24	1.3	19	1.7
No stool results available	198	10.7	136	12.1

Source: Appendix Table IIB, IIC, IVB and VA
N'= number of GE episodes reported
n (%)= number (percentage) of GE episodes within the specified category
*= due to quantity not sufficient or stool sample not tested

Supplement 88 Number of GE episodes and RV GE episodes reported from Dose 1 up to Visit 7, by severity using the 20-point Vesikari scale - Total vaccinated cohort

Event	Severity using Vesikari scale	HRV n	HRV %	Placebo n	Placebo %
GE	Mild (1-6)	926	50.1	444	39.5
	Moderate (7-10)	607	32.9	363	32.3
	Severe (≥11)	303	16.4	308	27.4
	Unknown	11	0.6	10	0.9
	Any	1847	100	1125	100
RV GE	Mild (1-6)	21	24.1	25	11.6
	Moderate (7-10)	42	48.3	58	27.0
	Severe (≥11)	24	27.6	132	61.4
	Any	87	100	215	100

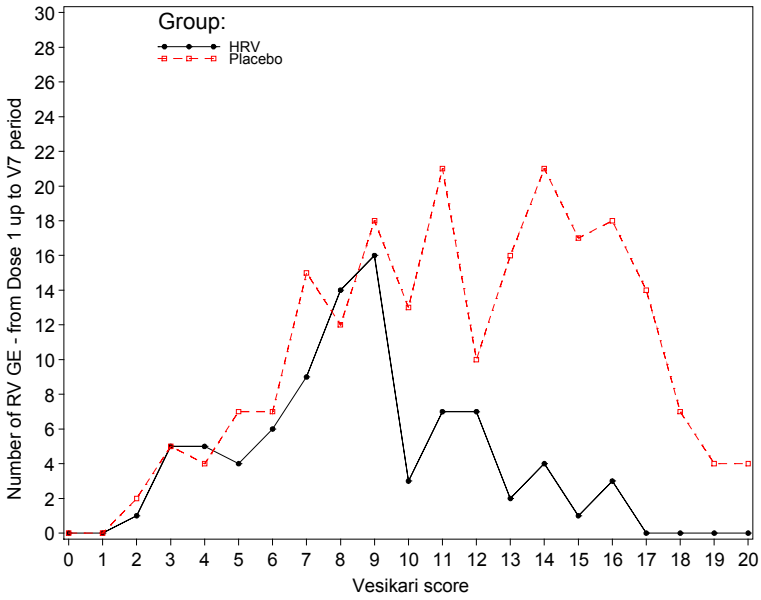
Source: Appendix Table IIB, IIC, IVB and VA
n (%) = number (percentage) of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported
Any = any specified symptom reported, regardless of Vesikari severity scale

Supplement 89 Number of GE episodes and RV GE episodes reported from Dose 1 up to Visit 7, by severity using the 24-point Clark scale - Total vaccinated cohort

Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	Mild (1-8)	1342	72.7	710	63.1
	Moderate (9-16)	478	25.9	352	31.3
	Severe (≥17)	12	0.6	48	4.3
	Unknown	15	0.8	15	1.3
	Any	1847	100	1125	100
RV GE	Mild (1-8)	41	47.1	65	30.2
	Moderate (9-16)	43	49.4	120	55.8
	Severe (≥17)	3	3.4	30	14.0
	Any	87	100	215	100

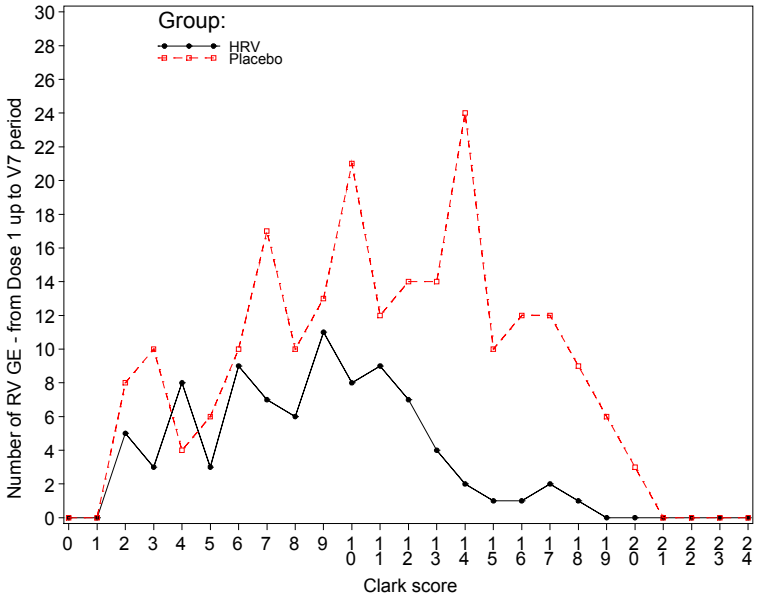
Source: Appendix Table IIB, IIC, IVB and VA
n (%) = number (percentage) of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported
Any = any specified symptom reported, regardless of Clark severity scale

Supplement 90 Distribution of Vesikari score for RV GE reported from Dose 1 up to Visit 7 – Total vaccinated cohort



Source: Appendix Table IIB, IIC, IVB and VA
V7 = Visit 7

Supplement 91 Distribution of Clark score for RV GE reported from Dose 1 up to Visit 7 – Total vaccinated cohort



Source: Appendix Table IIB, IIC, IVB and VA
V7 = Visit 7

Supplement 92 Percentage of subjects with RV GE episodes reported from Dose 1 up to Visit 7, by G serotype and P genotype - Total vaccinated cohort

Serotype	HRV N= 2646		Placebo N= 1348	
	n	%	n	%
Any	87	3.3	215	15.9
G1 wild type	18	0.7	91	6.8
G2	14	0.5	17	1.3
G3	4	0.2	12	0.9
G4	6	0.2	19	1.4
G9	39	1.5	77	5.7
GX	1	0.0	1	0.1
P4	16	0.6	16	1.2
P8 wild type	68	2.6	195	14.5
Unknown G type only*	2	0.1	0	0.0
Unknown P type only *	0	0.0	2	0.1
Unknown G and P type*	3	0.1	2	0.1

Source: Appendix Table IIB, IIC, IVB and VA
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
GX = G12
*=not typable

Supplement 93 Number of RV GE episodes reported from Dose 1 up to Visit 7, by G serotype and P genotype - Total vaccinated cohort

		HRV N' = 87		Placebo N' = 215	
Country	**Serotype**	**n**	**%**	**N**	**%**
Czech Republic	**G1WT+P8WT**	0	0.0	4	66.7
	G2+P4	1	33.3	1	16.7
	G4+P8WT	1	33.3	0	0.0
	G9+P8WT	0	0.0	1	16.7
	GX+P8WT	1	33.3	0	0.0
Finland	**G9+G1vac+P8WT+P8vac**	1	1.4	0	0.0
	G1WT+G4+P8WT	0	0.0	1	0.5
	G1WT+G9+P8WT	0	0.0	1	0.5
	G1WT and unknown P type*	0	0.0	1	0.5
	G1WT+G2+P4	0	0.0	1	0.5
	G1WT+P8WT	15	21.4	80	43.5
	G2 and unknown P type*	0	0.0	1	0.5
	G2+G9+P4	0	0.0	1	0.5
	G2+P4	12	17.1	12	6.5
	G3+P8WT	2	2.9	10	5.4
	G4+P8WT	4	5.7	17	9.2
	G9+P8WT	32	45.7	56	30.4
	GX+P8WT	0	0.0	1	0.5
	P4 and unknown G type*	1	1.4	0	0.0
	Unknown G and P type*	3	4.3	2	1.1
France	**G1WT+P8WT**	1	33.3	2	33.3
	G9+P8WT	2	66.7	4	66.7
Germany	**G1WT+P8WT**	1	33.3	1	50.0
	G2+P4	1	33.3	1	50.0
	G4+P8WT	1	33.3	0	0.0
Spain	**G1WT+P8WT**	1	12.5	0	0.0
	G3+P8WT	2	25.0	2	11.8
	G4+P8WT	0	0.0	1	5.9
	G9+P8WT	4	50.0	14	82.4
	P4 and unknown G type*	1	12.5	0	0.0
All countries	**G9+G1vac+P8WT+P8vac**	1	1.1	0	0.0
	G1WT+G4+P8WT	0	0.0	1	0.5
	G1WT+G9+P8WT	0	0.0	1	0.5
	G1WT and unknown P type*	0	0.0	1	0.5
	G1WT+G2+P4	0	0.0	1	0.5
	G1WT+P8WT	18	20.7	87	40.5
	G2 and unknown P type*	0	0.0	1	0.5
	G2+G9+P4	0	0.0	1	0.5
	G2+P4	14	16.1	14	6.5
	G3+P8WT	4	4.6	12	5.6
	G4+P8WT	6	6.9	18	8.4
	G9+P8WT	38	43.7	75	34.9
	GX+P8WT	1	1.1	1	0.5
	P4 and unknown G type*	2	2.3	0	0.0
	Unknown G and P type*	3	3.4	2	0.9

Source: Appendix Table IIB, IIC, IVB and VA

N'= number of RV GE episodes reported

n (%)= number (percentage) of RV GE episodes reported in each group, by G serotype and P genotype

wt=wild type; vac=vaccine strain; GX = G12; *=not typable

Supplement 94 Characteristics (based on Vesikari scale) of RV GE episodes reported from Dose 1 up to Visit 7 - Total vaccinated cohort

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

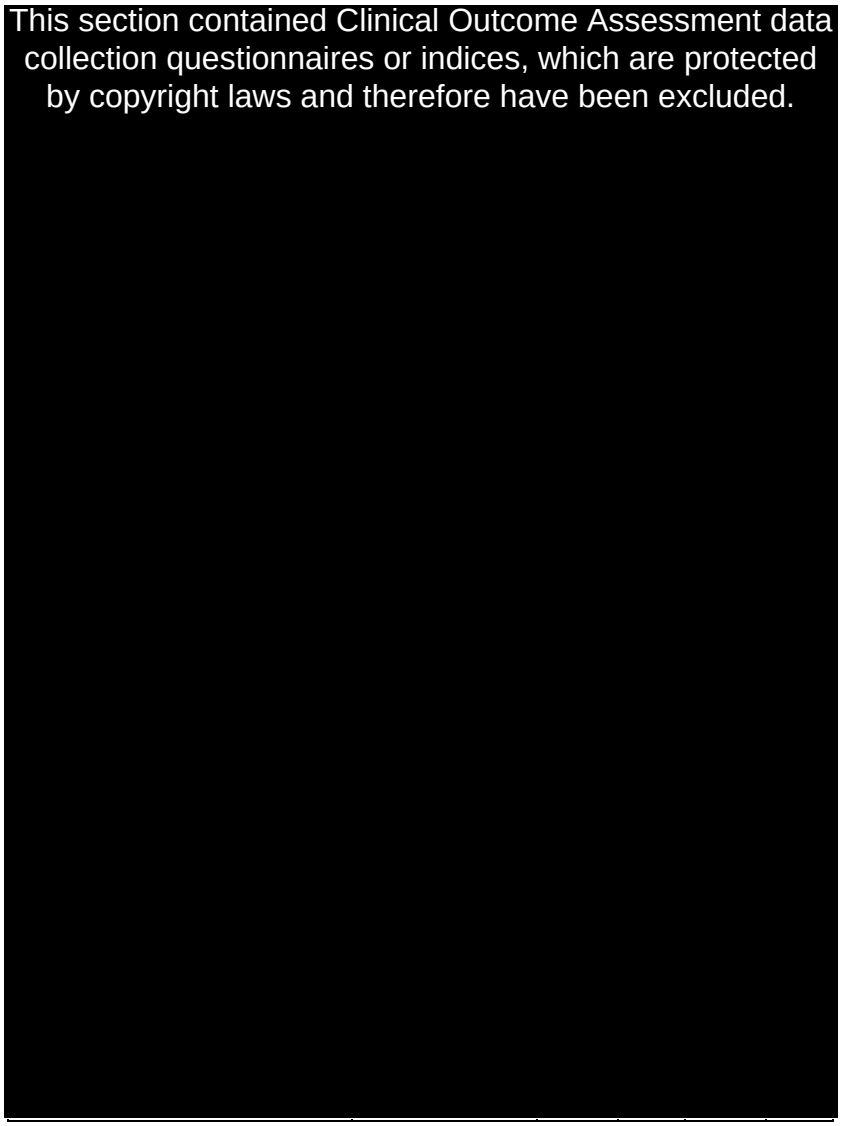
Source: Appendix Table IIB, IIC, IVB and VA
N'= number of RV GE episodes reported in each group
n (%) = number (percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 95 Characteristics (based on Vesikari scale) of RV GE episodes of G1 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

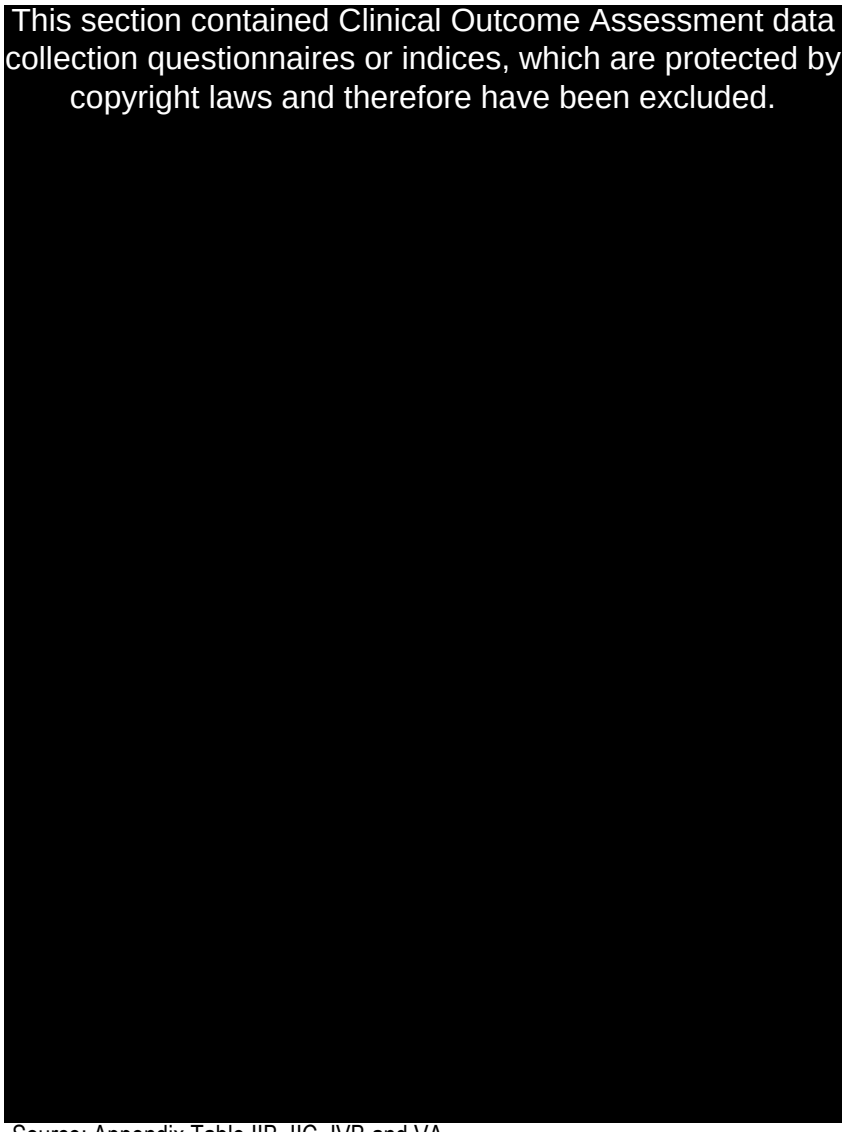
Source: Appendix Table IIB, IIC, IVB and VA
N'= number of RV GE episodes reported in each group
n (%) = number (percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 96 Characteristics (based on Vesikari scale) of RV GE episodes of G2 + P4 with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort



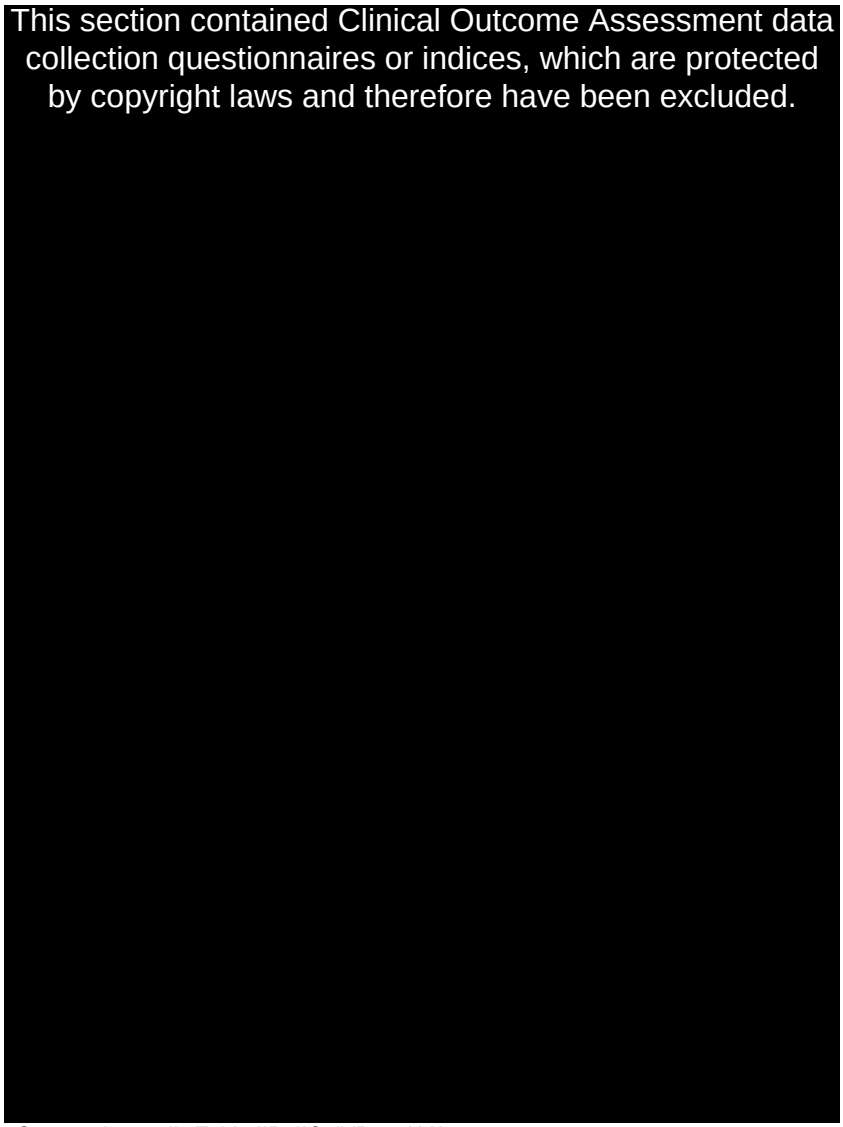
Source: Appendix Table IIB, IIC, IVB and VA
N'= number of RV GE episodes reported in each group
n (%) = number (percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 97 Characteristics (based on Vesikari scale) of RV GE episodes of G3 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort



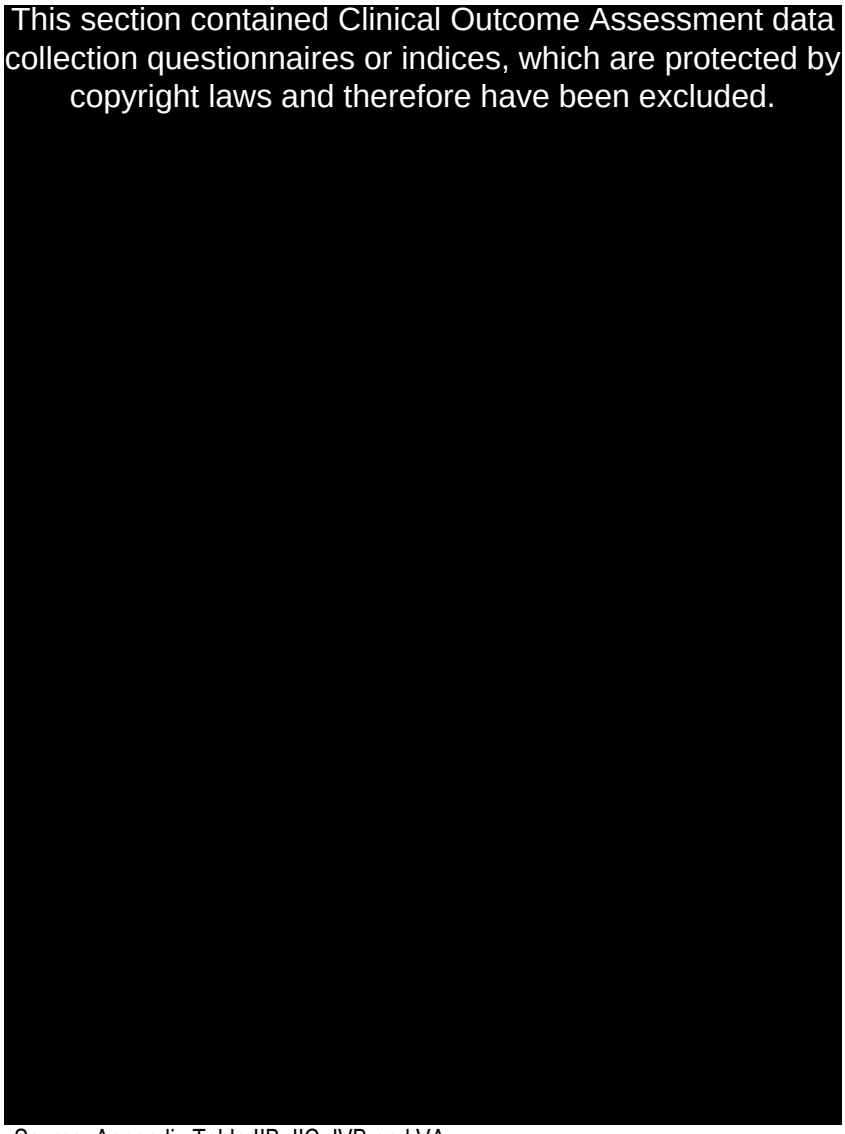
Source: Appendix Table IIB, IIC, IVB and VA
N'= number of RV GE episodes reported in each group
n (%) = number (percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 98 Characteristics (based on Vesikari scale) of RV GE episodes of G4 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort



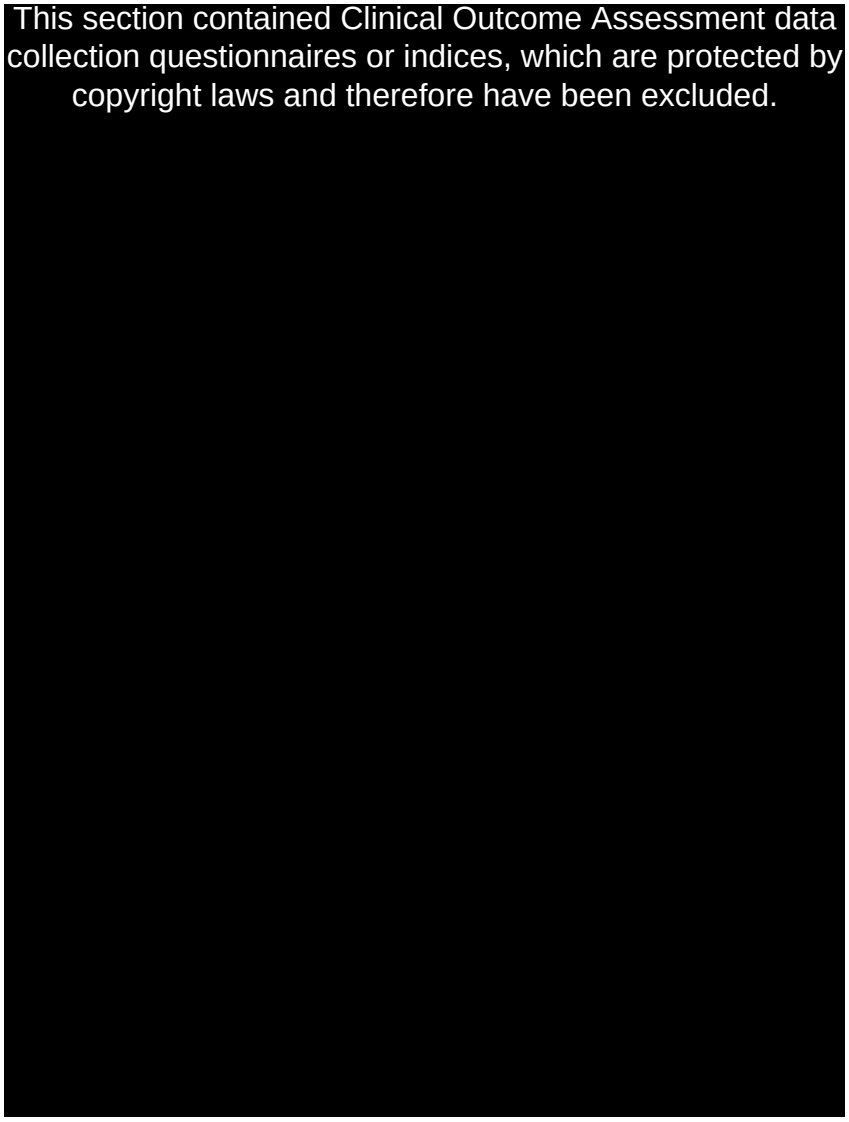
Source: Appendix Table IIB, IIC, IVB and VA
N'= number of RV GE episodes reported in each group
n (%) = number (percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 99 Characteristics (based on Vesikari scale) of RV GE episodes of G9 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort



Source: Appendix Table IIB, IIC, IVB and VA
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 100 Characteristics (based on Vesikari scale) of all cause GE episodes reported from Dose 1 up to Visit 7 - Total vaccinated cohort



Source: Appendix Table IIB, IIC and VA
N'= number of all cause 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 101 Characteristics (based on Clark scale) of RV GE episodes reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 87 Value or n	HRV N'= 87 %	Placebo N'= 215 Value or n	Placebo N'= 215 %
Severity Score	**Mean**	8.529	-	11.060	-
	SD	3.754	-	4.652	-
	Median	9.0	-	11.0	-
	Minimum	2	-	2	-
	Maximum	18	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	76	87.4	114	53.0
	5-7 days	11	12.6	94	43.7
	> 7 days	0	0.0	7	3.3
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	31	35.6	51	23.7
	5-7	38	43.7	70	32.6
	> 7	18	20.7	94	43.7
Duration of vomiting (days)	**0 - 1 day**	67	77.0	108	50.2
	2 days	15	17.2	52	24.2
	3-5 days	4	4.6	51	23.7
	> 5 days	1	1.1	4	1.9
Maximum number of episodes of Vomiting/24 hours	**0**	38	43.7	47	21.9
	1-3	39	44.8	105	48.8
	4-6	8	9.2	35	16.3
	> 6	2	2.3	28	13.0
Duration of fever (days)	**0 day**	36	41.4	65	30.2
	1-2 day	45	51.7	122	56.7
	3-4 days	6	6.9	26	12.1
	≥ 5 days	0	0.0	2	0.9
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	36	41.4	65	30.2
	38.0-38.2°C	8	9.2	13	6.0
	38.3-38.7°C	16	18.4	51	23.7
	≥ 38.8°C	27	31.0	86	40.0
Duration of behavioral symptoms	**0 day**	19	21.8	47	21.9
	1-2 days	41	47.1	86	40.0
	3-4 days	24	27.6	58	27.0
	≥ 5 days	3	3.4	24	11.2
Behavioral symptoms	**Behave as usual**	19	21.8	47	21.9
	Irritable/less playful	17	19.5	11	5.1
	Lethargic/listless	50	57.5	152	70.7
	Seizures	1	1.1	5	2.3

Source: Appendix Table IIB, IIC, IVB and VA

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 102 Characteristics (based on Clark scale) of RV GE episodes of G1 + P8 wild type with no other G type reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 18 Value or n	HRV N'= 18 %	Placebo N'= 87 Value or n	Placebo N'= 87 %
Severity Score	**Mean**	8.444	-	11.402	-
	SD	4.328	-	4.738	-
	Median	7.5	-	11.0	-
	Minimum	2	-	2	-
	Maximum	17	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	14	77.8	44	50.6
	5-7 days	4	22.2	41	47.1
	> 7 days	0	0.0	2	2.3
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	8	44.4	17	19.5
	5-7	7	38.9	30	34.5
	> 7	3	16.7	40	46.0
Duration of vomiting (days)	**0 - 1 day**	14	77.8	42	48.3
	2 days	4	22.2	17	19.5
	3-5 days	0	0.0	25	28.7
	> 5 days	0	0.0	3	3.4
Maximum number of episodes of Vomiting/24 hours	**0**	9	50.0	21	24.1
	1-3	8	44.4	39	44.8
	4-6	1	5.6	15	17.2
	> 6	0	0.0	12	13.8
Duration of fever (days)	**0 day**	8	44.4	26	29.9
	1-2 day	8	44.4	49	56.3
	3-4 days	2	11.1	11	12.6
	≥ 5 days	0	0.0	1	1.1
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	8	44.4	26	29.9
	38.0-38.2°C	4	22.2	5	5.7
	38.3-38.7°C	0	0.0	20	23.0
	≥ 38.8°C	6	33.3	36	41.4
Duration of behavioral symptoms	**0 day**	3	16.7	18	20.7
	1-2 days	5	27.8	31	35.6
	3-4 days	10	55.6	25	28.7
	≥ 5 days	0	0.0	13	14.9
Behavioral symptoms	**Behave as usual**	3	16.7	18	20.7
	Irritable/less playful	4	22.2	5	5.7
	Lethargic/listless	11	61.1	62	71.3
	Seizures	0	0.0	2	2.3

Source: Appendix Table IIB, IIC, IVB and VA

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 103 Characteristics (based on Clark scale) of RV GE episodes of G2 + P4 with no other G type reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 14 Value or n	HRV N'= 14 %	Placebo N'= 14 Value or n	Placebo N'= 14 %
Severity Score	**Mean**	8.286	-	8.000	-
	SD	3.604	-	5.505	-
	Median	9.0	-	6.5	-
	Minimum	2	-	2	-
	Maximum	15	-	18	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	13	92.9	10	71.4
	5-7 days	1	7.1	4	28.6
	> 7 days	0	0.0	0	0.0
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	7	50.0	6	42.9
	5-7	5	35.7	4	28.6
	> 7	2	14.3	4	28.6
Duration of vomiting (days)	**0 - 1 day**	11	78.6	8	57.1
	2 days	3	21.4	3	21.4
	3-5 days	0	0.0	3	21.4
	> 5 days	0	0.0	0	0.0
Maximum number of episodes of Vomiting/24 hours	**0**	6	42.9	6	42.9
	1-3	7	50.0	5	35.7
	4-6	1	7.1	2	14.3
	> 6	0	0.0	1	7.1
Duration of fever (days)	**0 day**	6	42.9	9	64.3
	1-2 day	7	50.0	5	35.7
	3-4 days	1	7.1	0	0.0
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	6	42.9	9	64.3
	38.0-38.2°C	0	0.0	0	0.0
	38.3-38.7°C	2	14.3	2	14.3
	≥ 38.8°C	6	42.9	3	21.4
Duration of behavioral symptoms	**0 day**	3	21.4	6	42.9
	1-2 days	8	57.1	5	35.7
	3-4 days	2	14.3	1	7.1
	≥ 5 days	1	7.1	2	14.3
Behavioral symptoms	**Behave as usual**	3	21.4	6	42.9
	Irritable/less playful	2	14.3	1	7.1
	Lethargic/listless	9	64.3	6	42.9
	Seizures	0	0.0	1	7.1

Source: Appendix Table IIB, IIC, IVB and VA

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 104 Characteristics (based on Clark scale) of RV GE episodes of G3 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 4 Value or n	HRV N'= 4 %	Placebo N'= 12 Value or n	Placebo N'= 12 %
Severity Score	**Mean**	5.500	-	10.833	-
	SD	4.041	-	3.664	-
	Median	5.5	-	11.0	-
	Minimum	2	-	3	-
	Maximum	9	-	16	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	4	100	6	50.0
	5-7 days	0	0.0	5	41.7
	> 7 days	0	0.0	1	8.3
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	2	50.0	3	25.0
	5-7	2	50.0	3	25.0
	> 7	0	0.0	6	50.0
Duration of vomiting (days)	**0 - 1 day**	3	75.0	6	50.0
	2 days	1	25.0	5	41.7
	3-5 days	0	0.0	1	8.3
	> 5 days	0	0.0	0	0.0
Maximum number of episodes of Vomiting/24 hours	**0**	3	75.0	2	16.7
	1-3	1	25.0	6	50.0
	4-6	0	0.0	3	25.0
	> 6	0	0.0	1	8.3
Duration of fever (days)	**0 day**	3	75.0	5	41.7
	1-2 day	1	25.0	6	50.0
	3-4 days	0	0.0	1	8.3
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	3	75.0	5	41.7
	38.0-38.2°C	0	0.0	0	0.0
	38.3-38.7°C	1	25.0	0	0.0
	≥ 38.8°C	0	0.0	7	58.3
Duration of behavioral symptoms	**0 day**	2	50.0	2	16.7
	1-2 days	0	0.0	7	58.3
	3-4 days	2	50.0	3	25.0
	≥ 5 days	0	0.0	0	0.0
Behavioral symptoms	**Behave as usual**	2	50.0	2	16.7
	Irritable/less playful	1	25.0	0	0.0
	Lethargic/listless	1	25.0	10	83.3
	Seizures	0	0.0	0	0.0

Source: Appendix Table IIB, IIC, IVB and VA

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 105 Characteristics (based on Clark scale) of RV GE episodes of G4 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 6 Value or n	HRV N'= 6 %	Placebo N'= 18 Value or n	Placebo N'= 18 %
Severity Score	**Mean**	8.833	-	11.222	-
	SD	3.189	-	4.453	-
	Median	9.0	-	10.5	-
	Minimum	5	-	2	-
	Maximum	14	-	20	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	6	100	9	50.0
	5-7 days	0	0.0	9	50.0
	> 7 days	0	0.0	0	0.0
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	2	33.3	6	33.3
	5-7	3	50.0	6	33.3
	> 7	1	16.7	6	33.3
Duration of vomiting (days)	**0 - 1 day**	5	83.3	10	55.6
	2 days	0	0.0	3	16.7
	3-5 days	1	16.7	4	22.2
	> 5 days	0	0.0	1	5.6
Maximum number of episodes of Vomiting/24 hours	**0**	2	33.3	4	22.2
	1-3	4	66.7	10	55.6
	4-6	0	0.0	2	11.1
	> 6	0	0.0	2	11.1
Duration of fever (days)	**0 day**	2	33.3	5	27.8
	1-2 day	3	50.0	11	61.1
	3-4 days	1	16.7	2	11.1
	≥ 5 days	0	0.0	0	0.0
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	2	33.3	5	27.8
	38.0-38.2°C	0	0.0	1	5.6
	38.3-38.7°C	3	50.0	3	16.7
	≥ 38.8°C	1	16.7	9	50.0
Duration of behavioral symptoms	**0 day**	0	0.0	2	11.1
	1-2 days	4	66.7	9	50.0
	3-4 days	2	33.3	6	33.3
	≥ 5 days	0	0.0	1	5.6
Behavioral symptoms	**Behave as usual**	0	0.0	2	11.1
	Irritable/less playful	4	66.7	0	0.0
	Lethargic/listless	2	33.3	16	88.9
	Seizures	0	0.0	0	0.0

Source: Appendix Table IIB, IIC, IVB and VA

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 106 Characteristics (based on Clark scale) of RV GE episodes of G9 + P8 wild type with no other Gtype reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 38 Value or n	HRV N'= 38 %	Placebo N'= 75 Value or n	Placebo N'= 75 %
Severity Score	**Mean**	9.079	-	11.440	-
	SD	3.752	-	4.509	-
	Median	9.5	-	12.0	-
	Minimum	2	-	2	-
	Maximum	18	-	19	-
Duration of looser than normal stools (days)	**0 day**	0	0.0	0	0.0
	1-4 days	33	86.8	38	50.7
	5-7 days	5	13.2	33	44.0
	> 7 days	0	0.0	4	5.3
Maximum number of looser than normal stools/24 hours	**0**	0	0.0	0	0.0
	2-4	10	26.3	16	21.3
	5-7	17	44.7	25	33.3
	> 7	11	28.9	34	45.3
Duration of vomiting (days)	**0 - 1 day**	30	78.9	36	48.0
	2 days	5	13.2	22	29.3
	3-5 days	2	5.3	17	22.7
	> 5 days	1	2.6	0	0.0
Maximum number of episodes of Vomiting/24 hours	**0**	16	42.1	11	14.7
	1-3	15	39.5	41	54.7
	4-6	6	15.8	13	17.3
	> 6	1	2.6	10	13.3
Duration of fever (days)	**0 day**	12	31.6	16	21.3
	1-2 day	24	63.2	47	62.7
	3-4 days	2	5.3	11	14.7
	≥ 5 days	0	0.0	1	1.3
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	12	31.6	16	21.3
	38.0-38.2°C	4	10.5	7	9.3
	38.3-38.7°C	9	23.7	25	33.3
	≥ 38.8°C	13	34.2	27	36.0
Duration of behavioral symptoms	**0 day**	9	23.7	16	21.3
	1-2 days	20	52.6	30	40.0
	3-4 days	7	18.4	21	28.0
	≥ 5 days	2	5.3	8	10.7
Behavioral symptoms	**Behave as usual**	9	23.7	16	21.3
	Irritable/less playful	5	13.2	5	6.7
	Lethargic/listless	23	60.5	52	69.3
	Seizures	1	2.6	2	2.7

Source: Appendix Table IIB, IIC, IVB and VA

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 107 Characteristics (based on Clark scale) of all cause GE episodes reported from Dose 1 up to Visit 7 - Total vaccinated cohort

Characteristics	Parameters or Categories	HRV N'= 1847 Value or n	HRV N'= 1847 %	Placebo N'= 1125 Value or n	Placebo N'= 1125 %
Severity Score	**Mean**	6.233	-	7.385	-
	SD	3.693	-	4.468	-
	Median	5.0	-	6.0	-
	Minimum	0	-	0	-
	Maximum	20	-	23	-
Duration of looser than normal stools (days)	**0 day**	17	0.9	16	1.4
	1-4 days	1302	70.5	738	65.6
	5-7 days	376	20.4	282	25.1
	> 7 days	152	8.2	89	7.9
Maximum number of looser than normal stools/24 hours	**0**	17	0.9	16	1.4
	2-4	758	41.0	392	34.8
	5-7	771	41.7	461	41.0
	> 7	301	16.3	256	22.8
Duration of vomiting (days)	**0 - 1 day**	1615	87.4	867	77.1
	2 days	132	7.1	134	11.9
	3-5 days	88	4.8	114	10.1
	> 5 days	12	0.6	10	0.9
Maximum number of episodes of Vomiting/24 hours	**0**	1248	67.6	650	57.8
	1-3	463	25.1	326	29.0
	4-6	103	5.6	93	8.3
	> 6	33	1.8	56	5.0
Duration of fever (days)	**0 day**	1334	72.2	708	62.9
	1-2 day	413	22.4	341	30.3
	3-4 days	82	4.4	67	6.0
	≥ 5 days	18	1.0	9	0.8
Maximum fever reported /24 hours (measured rectally)	**< 38.0°C**	1334	72.2	708	62.9
	38.0-38.2°C	110	6.0	69	6.1
	38.3-38.7°C	134	7.3	132	11.7
	≥ 38.8°C	269	14.6	216	19.2
Duration of behavioral symptoms	**0 day**	933	50.5	482	42.8
	1-2 days	612	33.1	395	35.1
	3-4 days	217	11.7	171	15.2
	≥ 5 days	85	4.6	77	6.8
Behavioral symptoms	**Behave as usual**	933	50.5	482	42.8
	Irritable/less playful	284	15.4	168	14.9
	Lethargic/listless	604	32.7	459	40.8
	Seizures	26	1.4	16	1.4

Source: Appendix Table IIB, IIC and VA

N'= number of all cause 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 108 Duration (in years) of the follow-up period from Dose 1 up Visit 7 - Total vaccinated cohort

Duration (years) of follow-up period	HRV N= 2646	Placebo N= 1348
Total	4310.2	2204.3
Mean	1.629	1.635
SD	0.187	0.183
Minimum	0.025	0.079
Q1	1.589	1.595
Median	1.655	1.668
Q3	1.718	1.723
Maximum	2.132	2.066

Source: Appendix Table IC
N = number of subjects included in each group
Total= sum of follow-up period expressed in year
SD= standard deviation
Q1= 25th percentile
Q3=75th percentile

Supplement 109 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	2646	87	3.3	2.6	4.0	79.4	73.4	84.1	<0.001
Placebo	1348	215	15.9	14.0	18.0				

Source: Appendix Table IIB, IIC, IVB and VA
N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 110 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by country - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	3	1.5	0.3	4.3	74.9	-17.6	95.9	0.065
	Placebo	100	6	6.0	2.2	12.6				
Finland	**HRV**	1918	70	3.6	2.9	4.6	80.7	74.5	85.6	<0.001
	Placebo	972	184	18.9	16.5	21.5				
France	**HRV**	95	3	3.2	0.7	9.0	73.2	-25.7	95.7	0.066
	Placebo	51	6	11.8	4.4	23.9				
Germany	**HRV**	190	3	1.6	0.3	4.5	21.8	-835.8	91.0	1.000
	Placebo	99	2	2.0	0.2	7.1				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	8	3.5	1.5	6.8	76.2	41.7	91.1	<0.001
	Placebo	116	17	14.7	8.8	22.4				

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 111 Percentage of subjects reporting any RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by RV serotype - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2646	18	0.7	0.4	1.1	89.9	83.2	94.3	<0.001
Placebo	1348	91	6.8	5.5	8.2				
G2									
HRV	2646	14	0.5	0.3	0.9	58.0	9.6	80.9	0.020
Placebo	1348	17	1.3	0.7	2.0				
G3									
HRV	2646	4	0.2	0.0	0.4	83.0	44.0	96.0	<0.001
Placebo	1348	12	0.9	0.5	1.5				
G4									
HRV	2646	6	0.2	0.1	0.5	83.9	58.1	94.7	<0.001
Placebo	1348	19	1.4	0.9	2.2				
G9									
HRV	2646	39	1.5	1.1	2.0	74.2	61.6	82.9	<0.001
Placebo	1348	77	5.7	4.5	7.1				
Pooled Non G1 (G2, G3, G4, G9, GX)									
HRV	2646	64	2.4	1.9	3.1	73.9	64.5	81.0	<0.001
Placebo	1348	125	9.3	7.8	10.9				

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified RV GE episode caused by the circulating wild-type RV in each group

GX = G12

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 112 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	24	0.9	0.6	1.3	90.7	85.6	94.3	<0.001
Placebo	1348	132	9.8	8.3	11.5				

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α = 0.05)

Supplement 113 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

Severity using Vesikari scale	Group	N	n	n/N	95%CI		Vaccine Efficacy	95%CI		P-value
				%	LL	UL	%	LL	UL	
≥11	HRV	2646	24	0.9	0.6	1.3	90.7	85.6	94.3	<0.001
	Placebo	1348	132	9.8	8.3	11.5				
≥12	HRV	2646	17	0.6	0.4	1.0	92.1	86.7	95.5	<0.001
	Placebo	1348	109	8.1	6.7	9.7				
≥13	HRV	2646	10	0.4	0.2	0.7	94.9	90.1	97.6	<0.001
	Placebo	1348	99	7.3	6.0	8.9				
≥14	HRV	2646	8	0.3	0.1	0.6	95.1	89.9	97.9	<0.001
	Placebo	1348	83	6.2	4.9	7.6				
≥15	HRV	2646	4	0.2	0.0	0.4	96.8	91.3	99.1	<0.001
	Placebo	1348	63	4.7	3.6	5.9				
≥16	HRV	2646	3	0.1	0.0	0.3	96.7	89.9	99.4	<0.001
	Placebo	1348	47	3.5	2.6	4.6				
≥17	HRV	2646	0	0.0	0.0	0.1	100.0	93.1	100.0	<0.001
	Placebo	1348	29	2.2	1.4	3.1				
≥18	HRV	2646	0	0.0	0.0	0.1	100.0	85.8	100.0	<0.001
	Placebo	1348	15	1.1	0.6	1.8				
≥19	HRV	2646	0	0.0	0.0	0.1	100.0	70.2	100.0	<0.001
	Placebo	1348	8	0.6	0.3	1.2				
≥20	HRV	2646	0	0.0	0.0	0.1	100.0	22.8	100.0	0.013
	Placebo	1348	4	0.3	0.1	0.8				

Source: Appendix Table IIB, IIC, IVB and VA

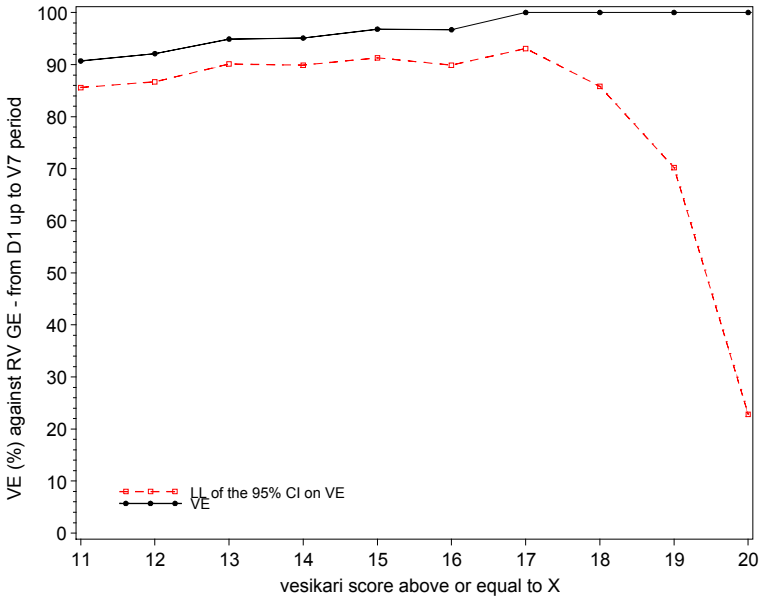
N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Vesikari scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 114 Vaccine efficacy against RV GE episodes with a score greater than or equal to X on the Vesikari scale from Dose 1 up to Visit 7 – Total vaccinated cohort



Source: Appendix Table IIB, IIC, IVB and VA
D1 = Dose 1
V7 = Visit 7

Supplement 115 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by country - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	0	0.0	0.0	1.8	100.0	-167.6	100.0	0.111
	Placebo	100	2	2.0	0.2	7.0				
Finland	**HRV**	1918	21	1.1	0.7	1.7	90.9	85.4	94.6	<0.001
	Placebo	972	117	12.0	10.1	14.2				
France	**HRV**	95	1	1.1	0.0	5.7	82.1	-122.9	99.7	0.123
	Placebo	51	3	5.9	1.2	16.2				
Germany	**HRV**	190	0	0.0	0.0	1.9	-	-	-	-
	Placebo	99	0	0.0	0.0	3.7				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	2	0.9	0.1	3.1	89.9	52.5	98.9	<0.001
	Placebo	116	10	8.6	4.2	15.3				

Source: Appendix Table IIB, IIC, IVB and VA
N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 116 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by RV serotype - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2646	4	0.2	0.0	0.4	96.5	90.5	99.1	<0.001
Placebo	1348	58	4.3	3.3	5.5				
G2									
HRV	2646	2	0.1	0.0	0.3	85.4	23.6	98.5	0.009
Placebo	1348	7	0.5	0.2	1.1				
G3									
HRV	2646	1	0.0	0.0	0.2	94.3	59.1	99.9	<0.001
Placebo	1348	9	0.7	0.3	1.3				
G4									
HRV	2646	1	0.0	0.0	0.2	95.4	68.1	99.9	<0.001
Placebo	1348	11	0.8	0.4	1.5				
G9									
HRV	2646	13	0.5	0.3	0.8	85.9	73.5	93.0	<0.001
Placebo	1348	47	3.5	2.6	4.6				
Pooled Non G1 (G2, G3, G4, G9, GX)									
HRV	2646	17	0.6	0.4	1.0	88.3	80.0	93.5	<0.001
Placebo	1348	74	5.5	4.3	6.8				

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified severe RV GE episode caused by the circulating wild-type RV in each group

GX = G12

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 117 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	3	0.1	0.0	0.3	94.9	83.6	99.0	<0.001
Placebo	1348	30	2.2	1.5	3.2				

Source: Appendix Table IIB, IIC, IVB and VA

n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 118 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Clark scale and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

Severity using Clark scale	Group	N	n	n/N	95%CI		Vaccine Efficacy	95%CI		P-value
				%	LL	UL	%	LL	UL	
≥17	HRV	2646	3	0.1	0.0	0.3	94.9	83.6	99.0	<0.001
	Placebo	1348	30	2.2	1.5	3.2				
≥18	HRV	2646	1	0.0	0.0	0.2	97.2	82.1	99.9	<0.001
	Placebo	1348	18	1.3	0.8	2.1				
≥19	HRV	2646	0	0.0	0.0	0.1	100.0	74.2	100.0	<0.001
	Placebo	1348	9	0.7	0.3	1.3				
≥20	HRV	2646	0	0.0	0.0	0.1	100.0	-23.3	100.0	0.038
	Placebo	1348	3	0.2	0.0	0.6				
≥21	HRV	2646	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1348	0	0.0	0.0	0.3				
≥22	HRV	2646	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1348	0	0.0	0.0	0.3				
≥23	HRV	2646	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1348	0	0.0	0.0	0.3				
≥24	HRV	2646	0	0.0	0.0	0.1	-	-	-	-
	Placebo	1348	0	0.0	0.0	0.3				

Source: Appendix Table IIB, IIC, IVB and VA

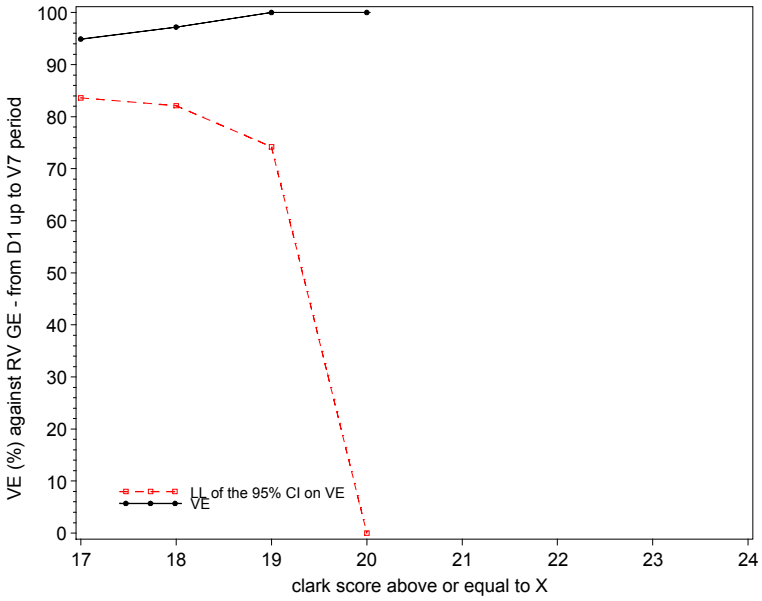
N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Clark scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 119 Vaccine efficacy against RV GE episodes with a score greater than or equal to X on the Clark scale from Dose 1 up to Visit 7 – Total vaccinated cohort



Source: Appendix Table IIB, IIC, IVB and VA
D1 = Dose 1; V7 = Visit 7
Y-axis has been cut at 0

Supplement 120 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by country - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	0	0.0	0.0	1.8	-	-	-	-
	Placebo	100	0	0.0	0.0	3.6				
Finland	**HRV**	1918	3	0.2	0.0	0.5	94.2	80.9	98.9	<0.001
	Placebo	972	26	2.7	1.8	3.9				
France	**HRV**	95	0	0.0	0.0	3.8	100.0	-1993.7	100.0	0.349
	Placebo	51	1	2.0	0.0	10.4				
Germany	**HRV**	190	0	0.0	0.0	1.9	-	-	-	-
	Placebo	99	0	0.0	0.0	3.7				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	0	0.0	0.0	1.6	100.0	-22.6	100.0	0.037
	Placebo	116	3	2.6	0.5	7.4				

Source: Appendix Table IIB, IIC, IVB and VA
N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one severe RV GE episode caused by the circulating wild-type RV in each group
95% CI, LL, UL = Lower and upper limits of the 95% confidence interval
P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 121 Percentage of subjects reporting severe (Clark score greater than 16) RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by RV serotype - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 wild-type									
HRV	2646	1	0.0	0.0	0.2	96.4	76.1	99.9	<0.001
Placebo	1348	14	1.0	0.6	1.7				
G2									
HRV	2646	0	0.0	0.0	0.1	100.0	-1886.8	100.0	0.338
Placebo	1348	1	0.1	0.0	0.4				
G3									
HRV	2646	0	0.0	0.0	0.1	-	-	-	-
Placebo	1348	0	0.0	0.0	0.3				
G4									
HRV	2646	0	0.0	0.0	0.1	100.0	-171.3	100.0	0.114
Placebo	1348	2	0.1	0.0	0.5				
G9									
HRV	2646	2	0.1	0.0	0.3	92.2	65.4	99.1	<0.001
Placebo	1348	13	1.0	0.5	1.6				
Pooled Non G1 (G2, G4, G9)									
HRV	2646	2	0.1	0.0	0.3	93.6	72.9	99.3	<0.001
Placebo	1348	16	1.2	0.7	1.9				

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one specified severe RV GE episode caused by the circulating wild-type RV in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 122 Percentage of subjects reporting all cause GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by country and for all countries - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	199	89	44.7	37.7	51.9	4.8	-38.5	33.9	0.714
	Placebo	100	47	47.0	36.9	57.2				
Finland	HRV	1918	938	48.9	46.6	51.2	13.7	4.0	22.4	<0.001
	Placebo	972	551	56.7	53.5	59.8				
France	HRV	95	42	44.2	34.0	54.8	16.5	-40.8	49.7	0.385
	Placebo	51	27	52.9	38.5	67.1				
Germany	HRV	190	36	18.9	13.6	25.3	14.7	-52.1	51.2	0.538
	Placebo	99	22	22.2	14.5	31.7				
Italy	HRV	15	4	26.7	7.8	55.1	-infinity	-infinity	56.0	0.125
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	229	110	48.0	41.4	54.7	19.2	-10.8	40.8	0.053
	Placebo	116	69	59.5	50.0	68.5				
All countries	HRV	2646	1219	46.1	44.2	48.0	13.3	4.7	21.0	<0.001
	Placebo	1348	716	53.1	50.4	55.8				

Source: Appendix Table IIB, IIC and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 123 Percentage of subjects reporting all cause severe (Vesikari scale) GE episodes and vaccine efficacy from Dose 1 up to Visit 7, by country and for all countries - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	HRV	199	20	10.1	6.2	15.1	-11.7	-178.5	51.4	0.839
	Placebo	100	9	9.0	4.2	16.4				
Finland	HRV	1918	214	11.2	9.8	12.7	50.7	40.2	59.4	<0.001
	Placebo	972	220	22.6	20.0	25.4				
France	HRV	95	5	5.3	1.7	11.9	66.4	-16.3	91.4	0.063
	Placebo	51	8	15.7	7.0	28.6				
Germany	HRV	190	3	1.6	0.3	4.5	73.9	-22.0	95.8	0.067
	Placebo	99	6	6.1	2.3	12.7				
Italy	HRV	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	HRV	229	34	14.8	10.5	20.1	36.2	-9.9	62.6	0.072
	Placebo	116	27	23.3	15.9	32.0				
All countries	HRV	2646	276	10.4	9.3	11.7	47.9	38.2	56.1	<0.001
	Placebo	1348	270	20.0	17.9	22.3				

Source: Appendix Table IIB, IIC and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one severe GE episode regardless of any cause in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 124 Percentage of subjects hospitalized due to RV GE episodes and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	2	0.1	0.0	0.3	95.9	83.7	99.5	<0.001
Placebo	1348	25	1.9	1.2	2.7				

Source: Appendix Table IIB, IIC, IVB and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects hospitalized due to RV GE episode caused by the circulating wild-type RV

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 125 Percentage of subjects hospitalized due to GE episodes and vaccine efficacy from Dose 1 up to Visit 7 - Total vaccinated cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	2646	29	1.1	0.7	1.6	71.0	53.4	82.3	<0.001
Placebo	1348	51	3.8	2.8	4.9				

Source: Appendix Table IIB, IIC and VA

N = number of subjects included in each group

n (%) = number (percentage) of subjects hospitalized due to GE episode

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 126 Percentage of subjects reporting any RV GE episodes requiring medical attention and vaccine efficacy from Dose 1 up to Visit 7, by country and for all countries - Total vaccinated cohort

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Czech Republic	**HRV**	199	3	1.5	0.3	4.3	74.9	-17.6	95.9	0.065
	Placebo	100	6	6.0	2.2	12.6				
Finland	**HRV**	1918	25	1.3	0.8	1.9	88.3	81.7	92.7	<0.001
	Placebo	972	108	11.1	9.2	13.3				
France	**HRV**	95	3	3.2	0.7	9.0	67.8	-65.6	95.0	0.128
	Placebo	51	5	9.8	3.3	21.4				
Germany	**HRV**	190	3	1.6	0.3	4.5	21.8	-835.8	91.0	1.000
	Placebo	99	2	2.0	0.2	7.1				
Italy	**HRV**	15	0	0.0	0.0	21.8	-	-	-	-
	Placebo	10	0	0.0	0.0	30.8				
Spain	**HRV**	229	8	3.5	1.5	6.8	74.7	37.3	90.6	0.001
	Placebo	116	16	13.8	8.1	21.4				
All countries	**HRV**	2646	42	1.6	1.1	2.1	84.4	77.8	89.2	<0.001
	Placebo	1348	137	10.2	8.6	11.9				

Source: Appendix Table IIB, IIC, IVB and VA

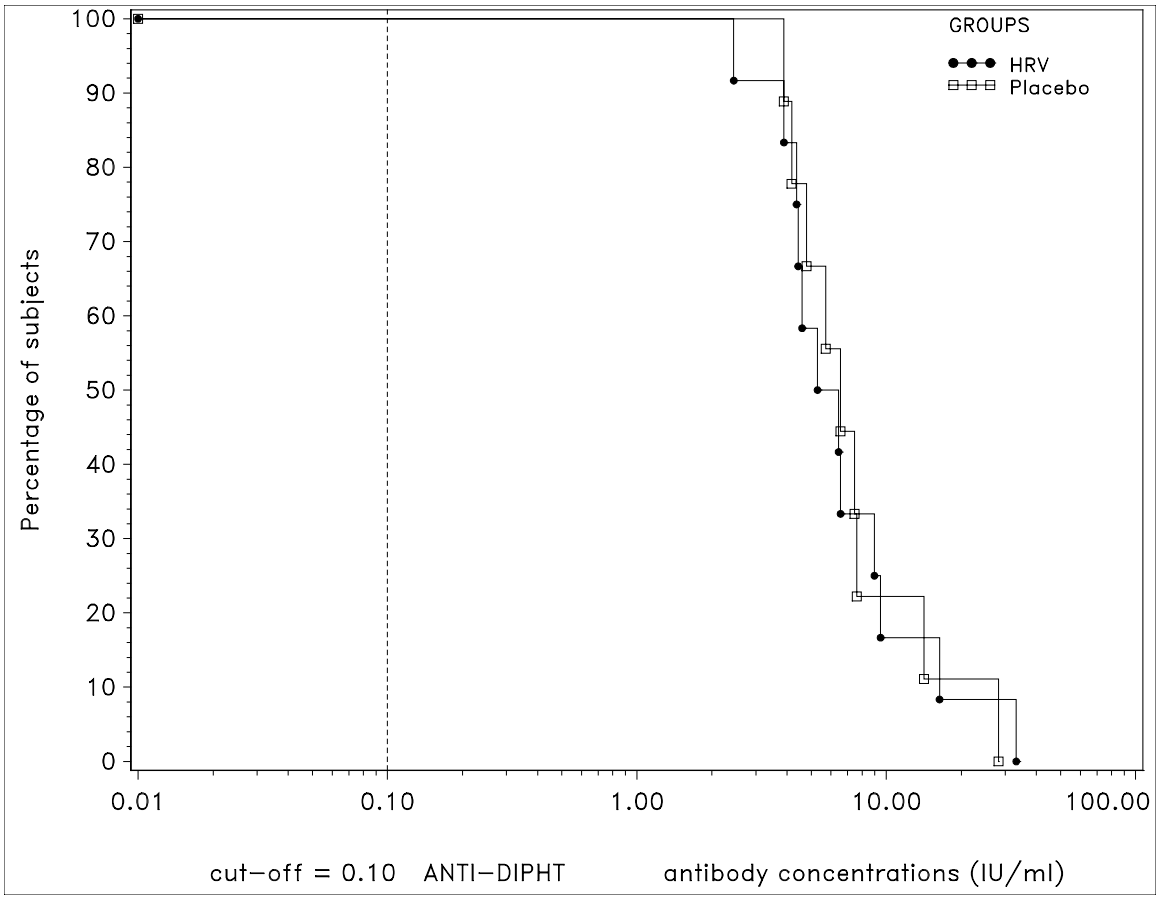
N = number of subjects included in each group

n (%) = number (percentage) of subjects reporting at least one RV GE episode caused by the circulating wild-type RV requiring medical attention in each group

95% CI, LL, UL = Lower and upper limits of the 95% confidence interval

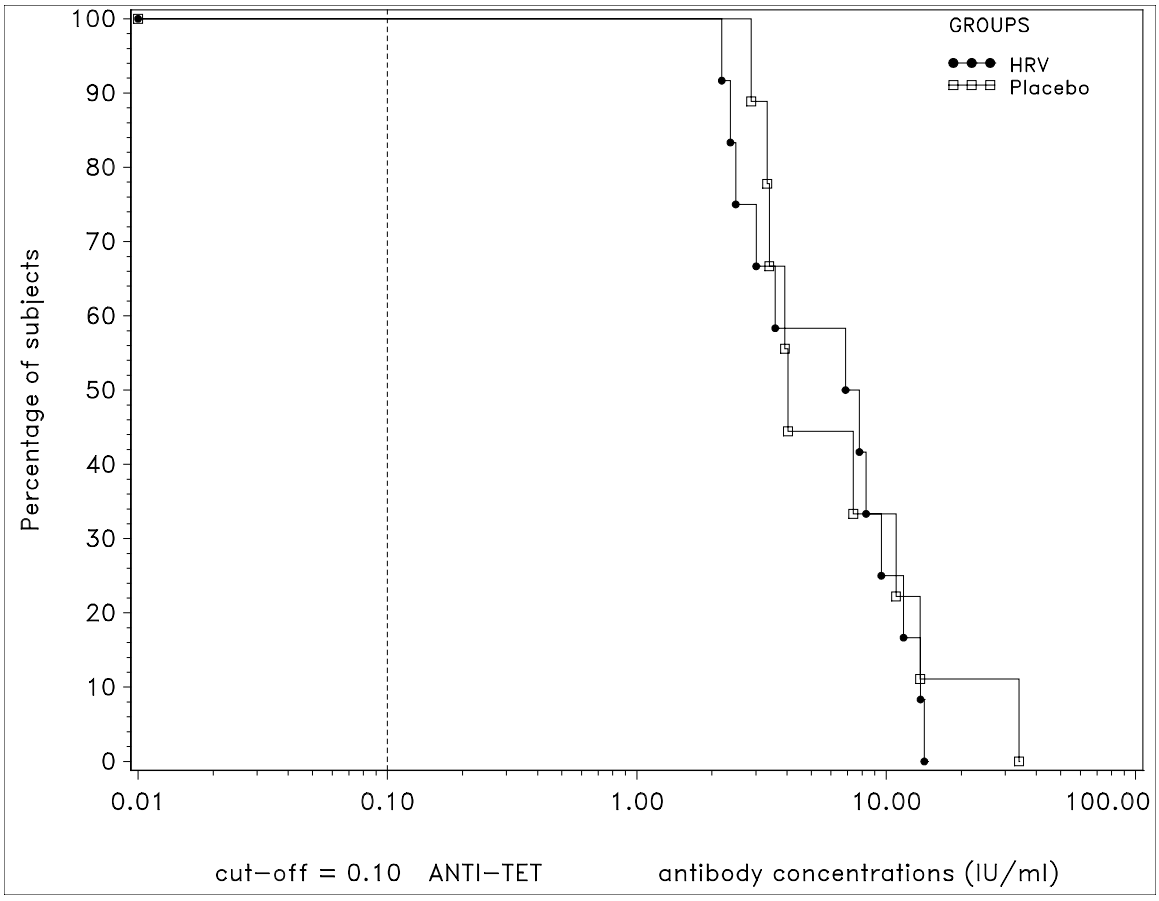
P-value=two-sided Fisher's exact test (significant level of α=0.05)

Supplement 127 Reverse cumulative curves for anti-diphtheria antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



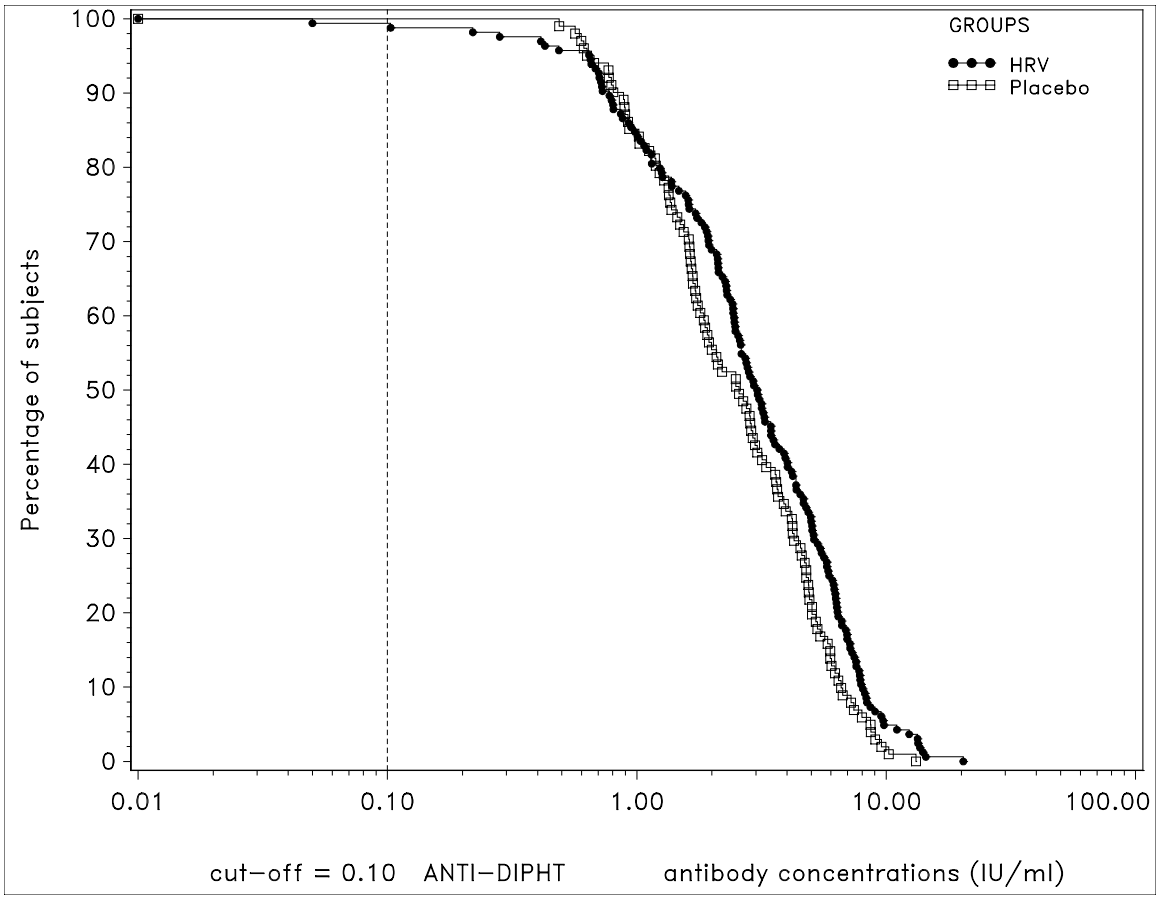
Data source = Appendix table IIIA

Supplement 128 Reverse cumulative curves for anti-tetanus antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



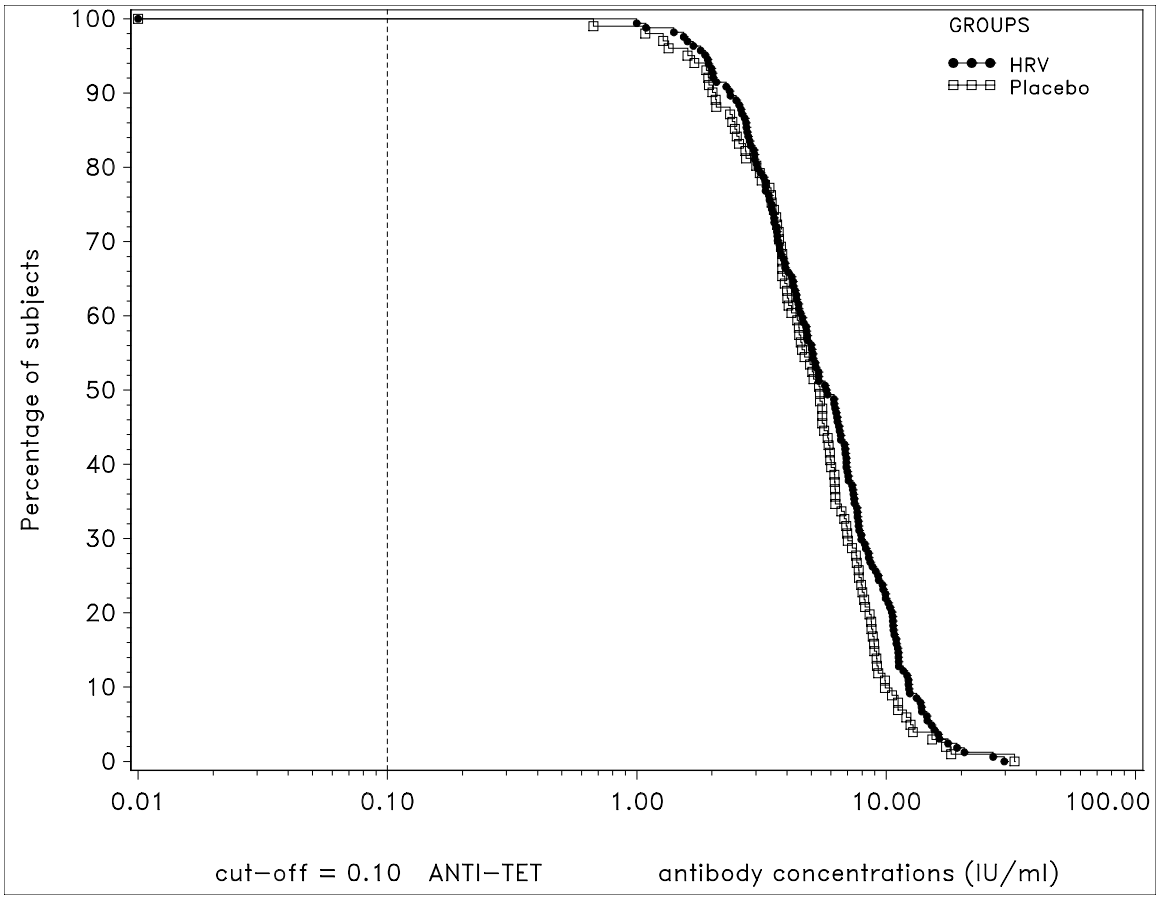
Data source = Appendix table IIIA

Supplement 129 Reverse cumulative curves for anti-diphtheria antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



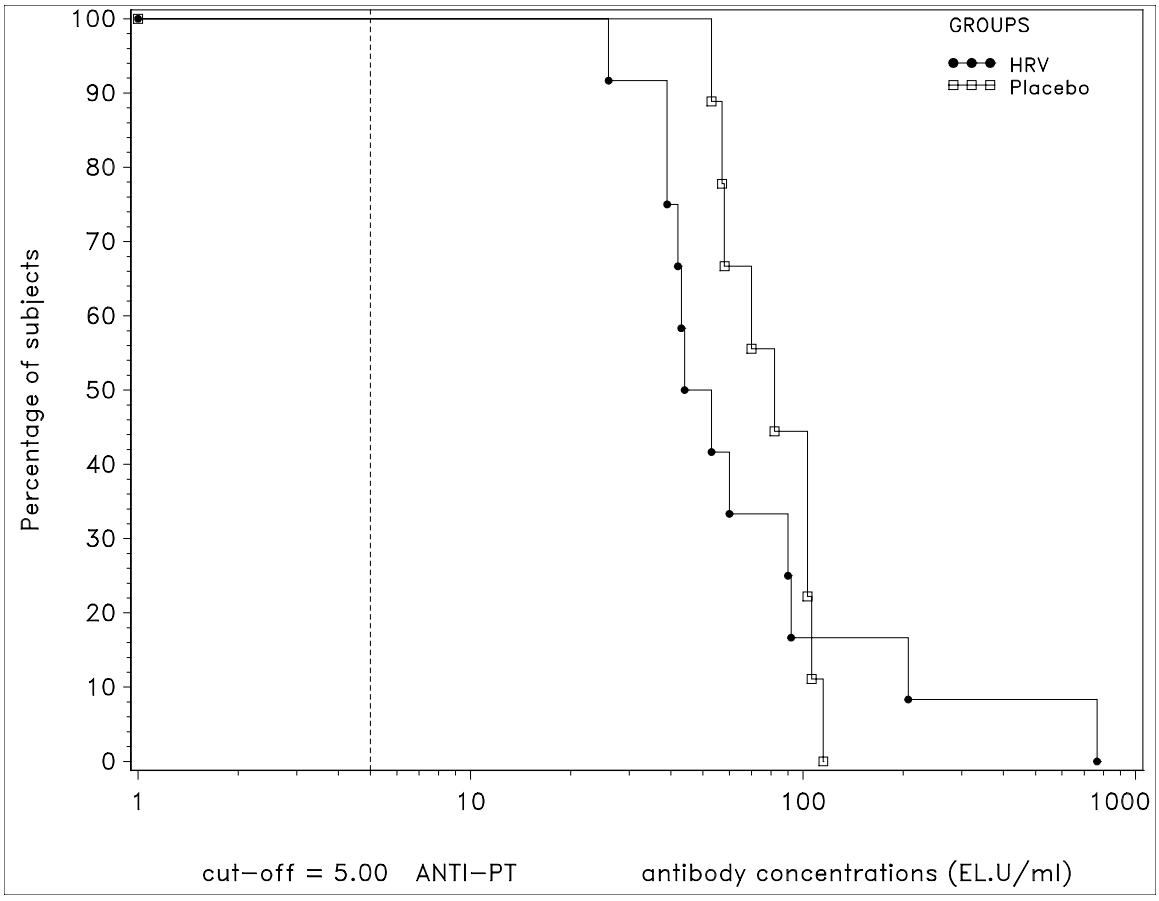
Data source = Appendix table IIIA

Supplement 130 Reverse cumulative curves for anti-tetanus antibody concentrations at post dose 3 (Visit 5/ 6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



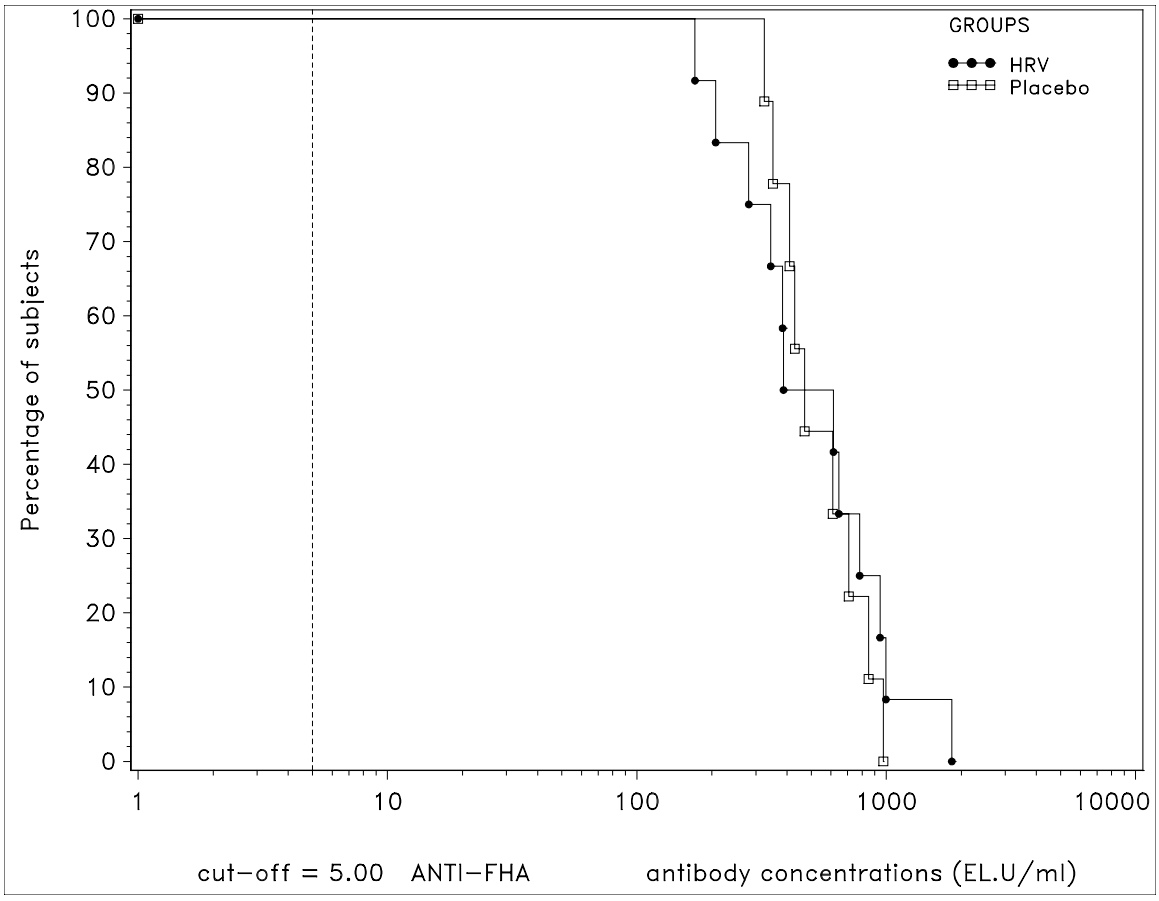
Data source = Appendix table IIIA

Supplement 131 Reverse cumulative curves for anti-PT antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



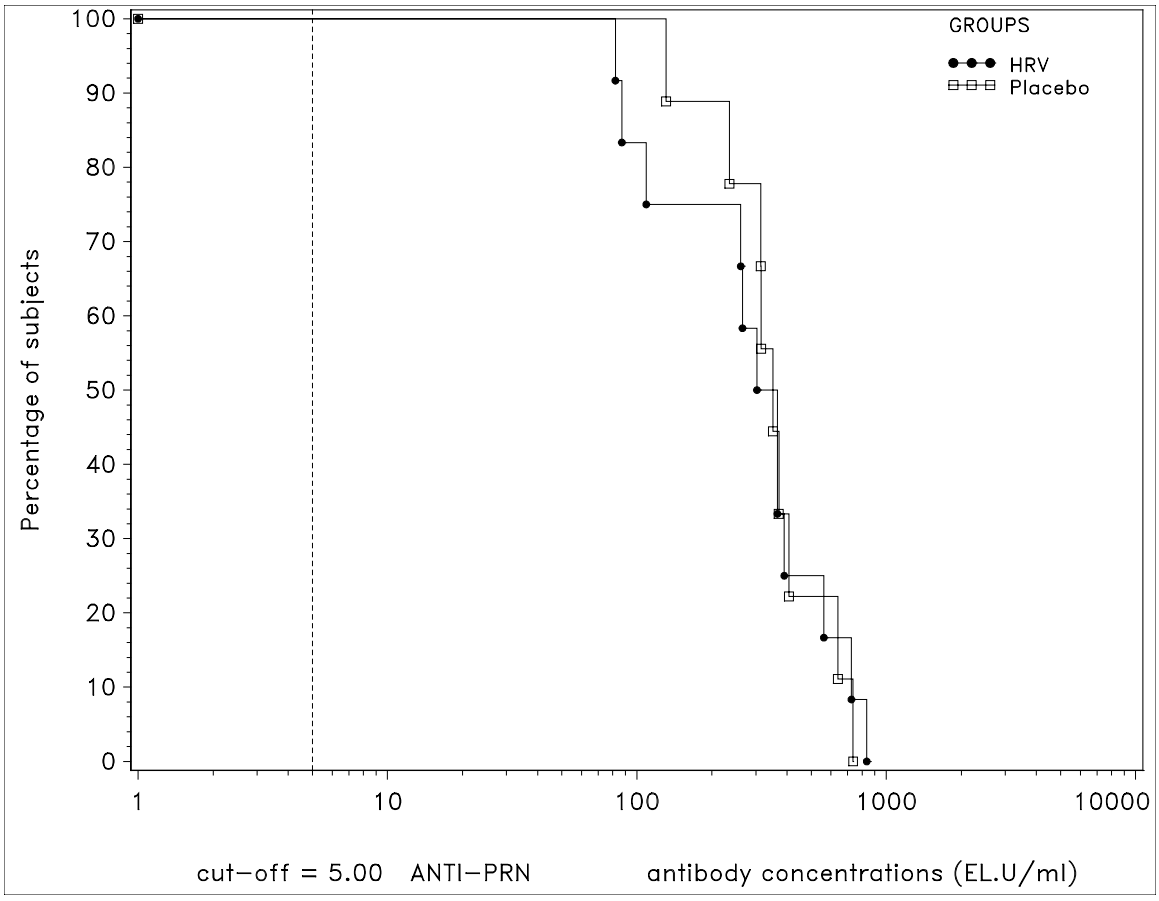
Data source = Appendix table IIIA

Supplement 132 Reverse cumulative curves for anti-FHA antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



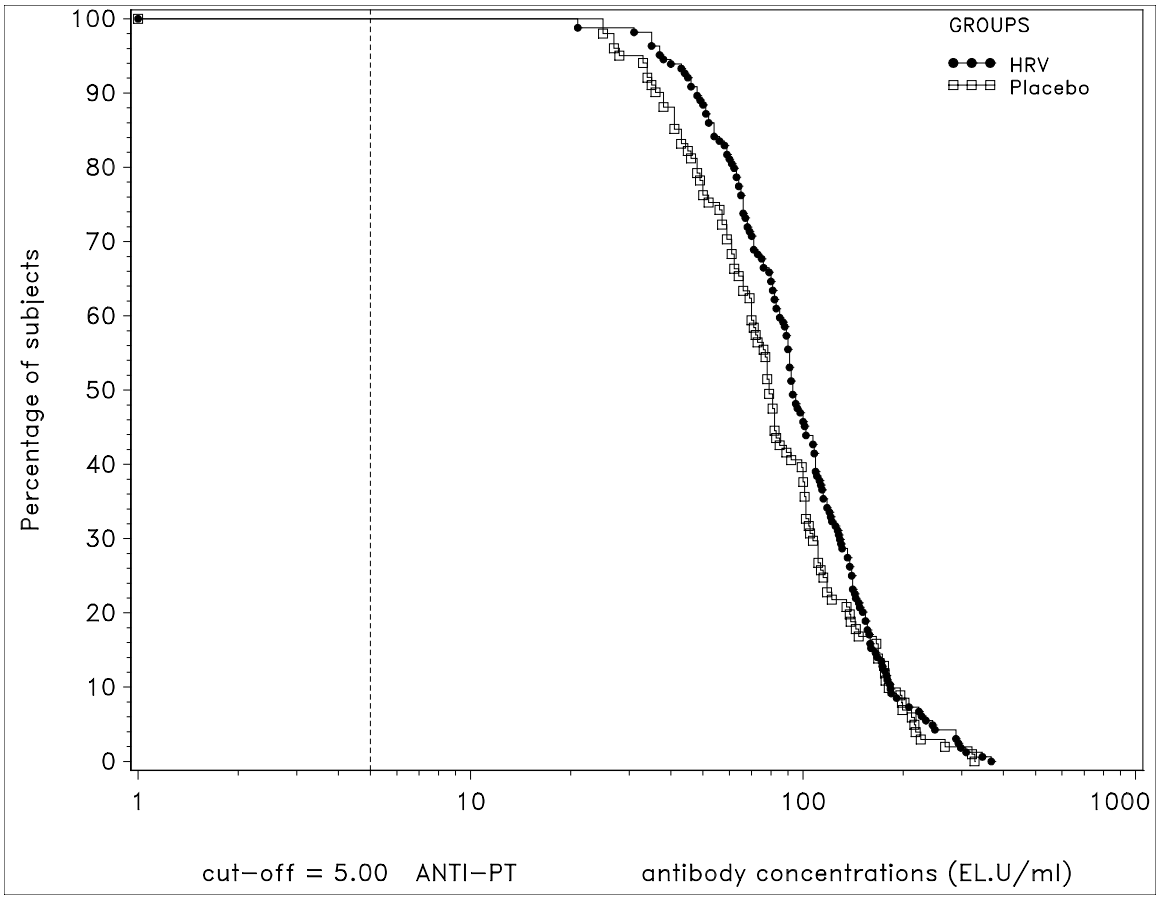
Data source = Appendix table IIIA

Supplement 133 Reverse cumulative curves for anti-PRN antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



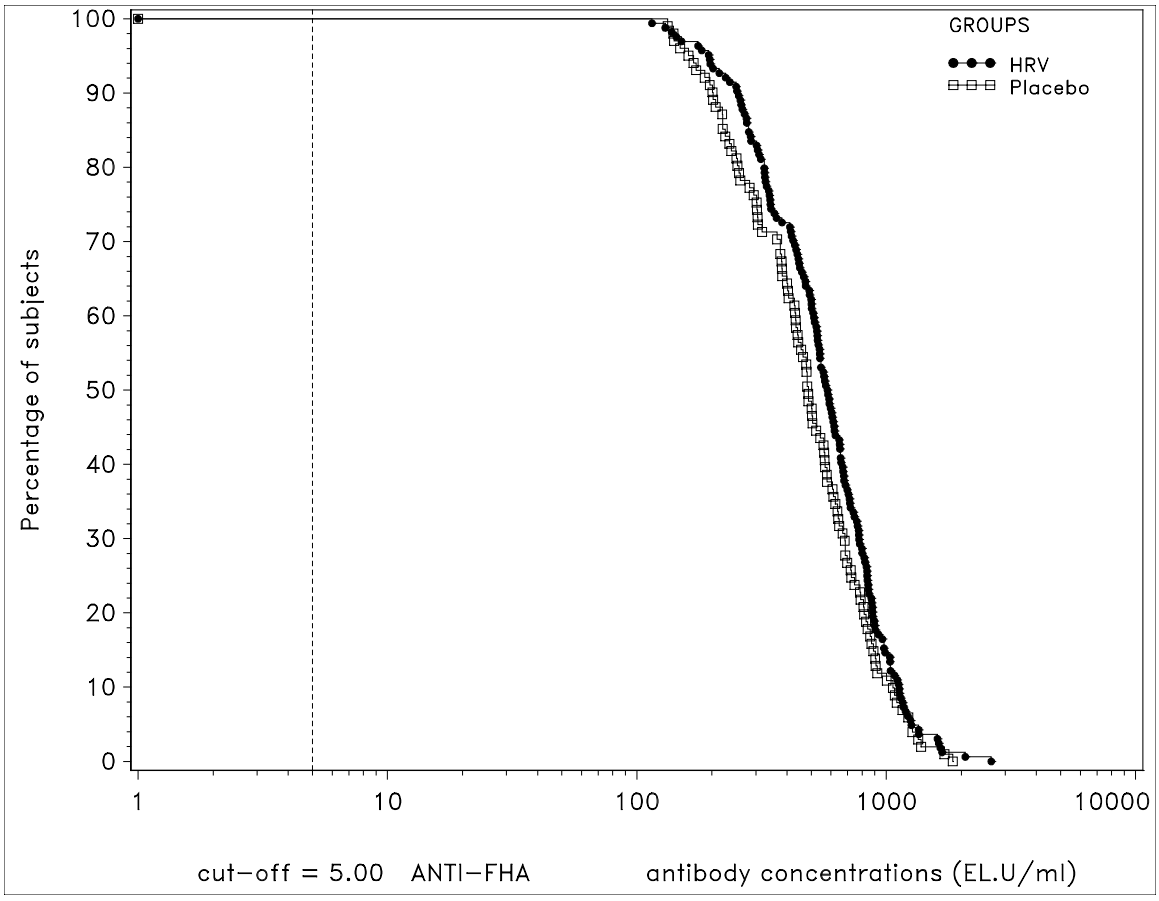
Data source = Appendix table IIIA

Supplement 134 Reverse cumulative curves for anti-PT antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



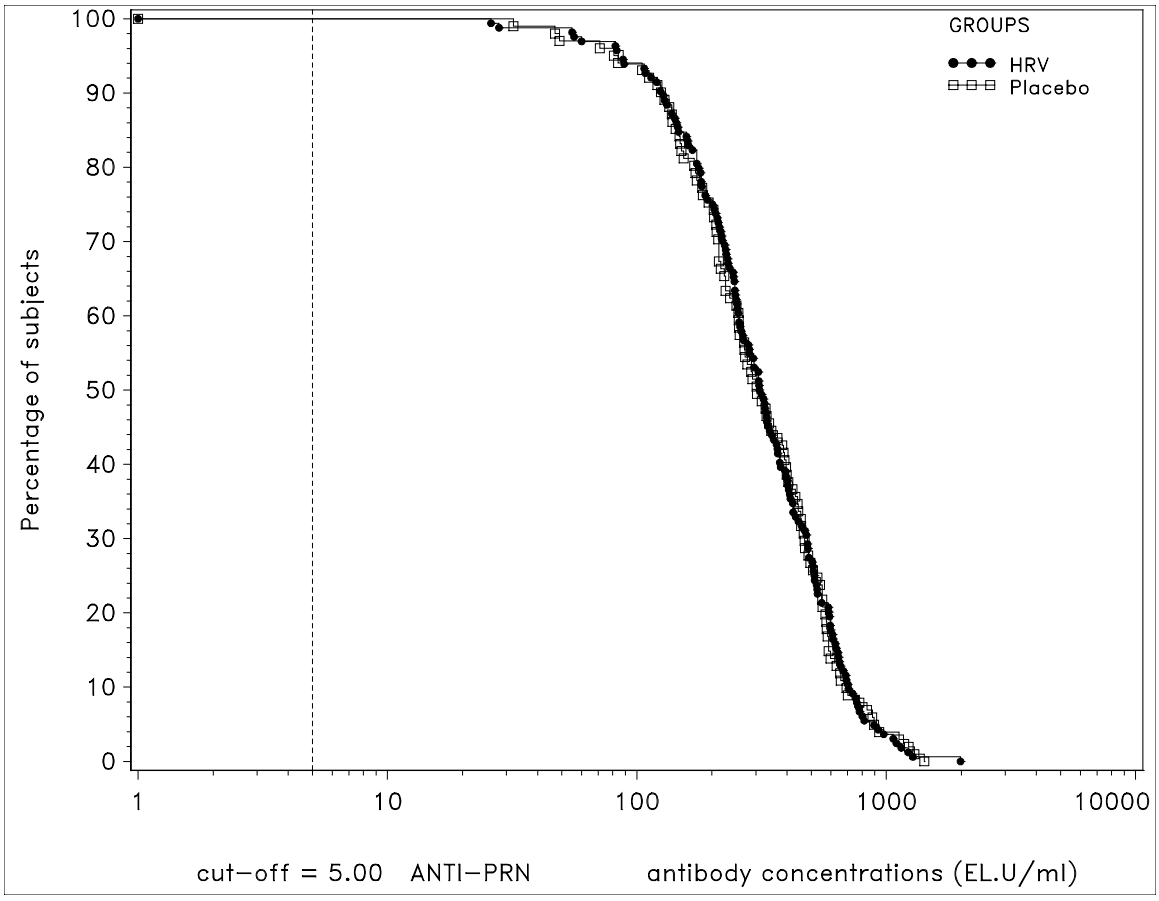
Data source = Appendix table IIIA

Supplement 135 Reverse cumulative curves for anti-FHA antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



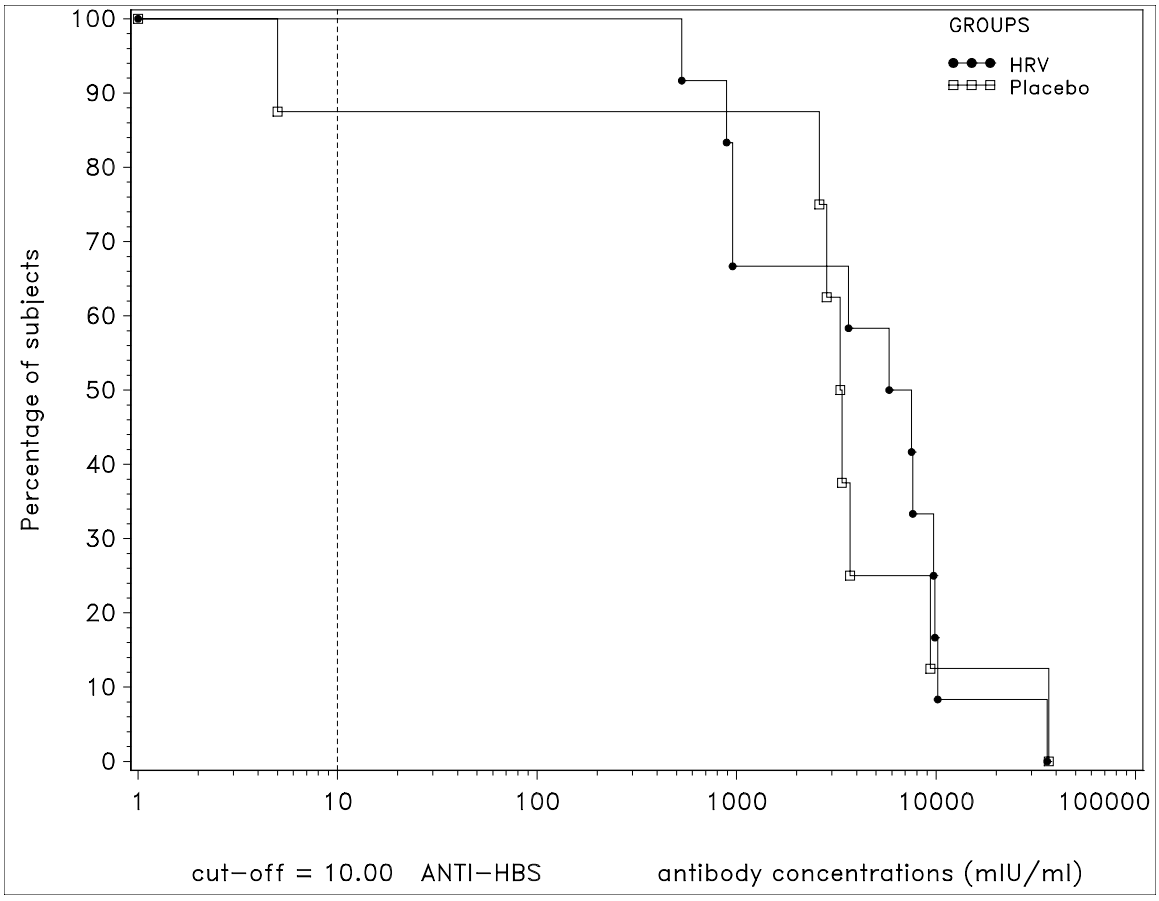
Data source = Appendix table IIIA

Supplement 136 Reverse cumulative curves for anti-PRN antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



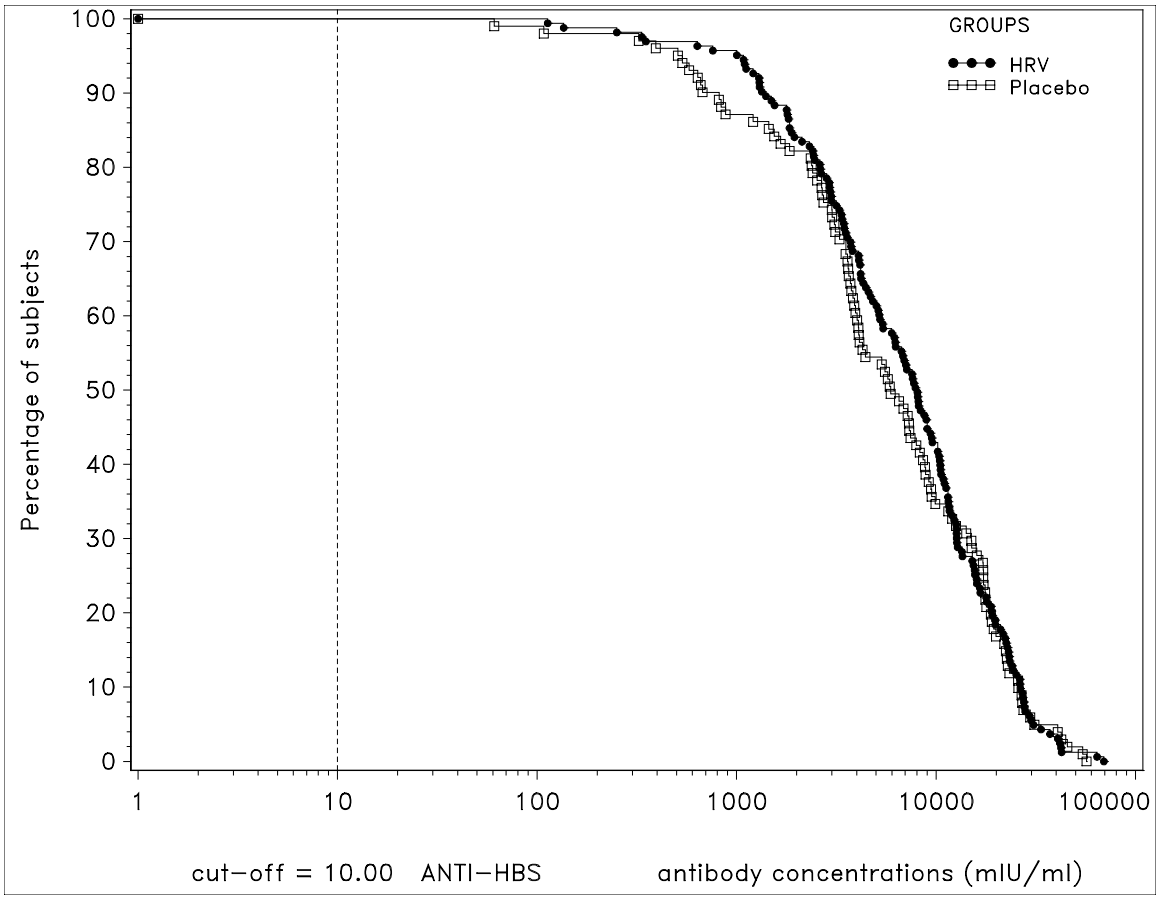
Data source = Appendix table IIIA

Supplement 137 Reverse cumulative curves for anti-HBS antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



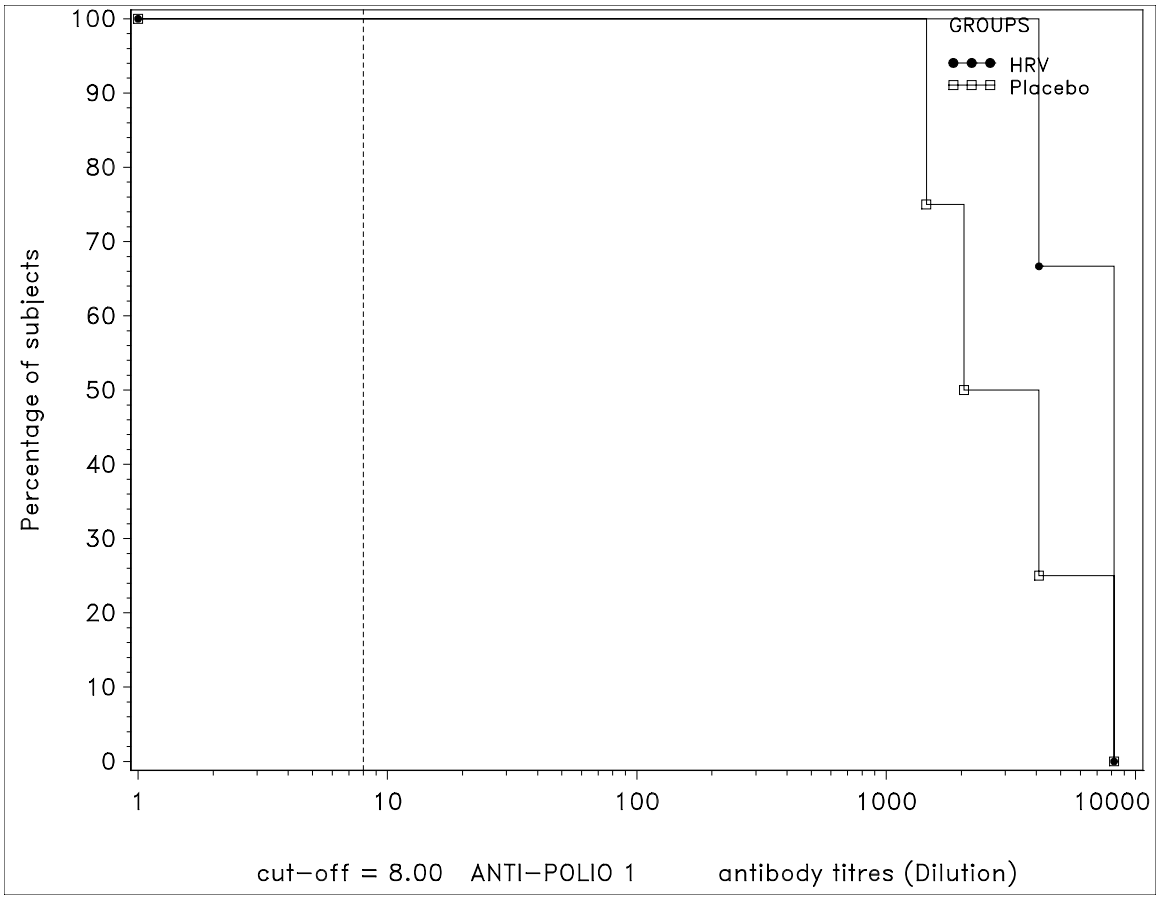
Data source = Appendix table IIIA

Supplement 138 Reverse cumulative curves for anti-HBS antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



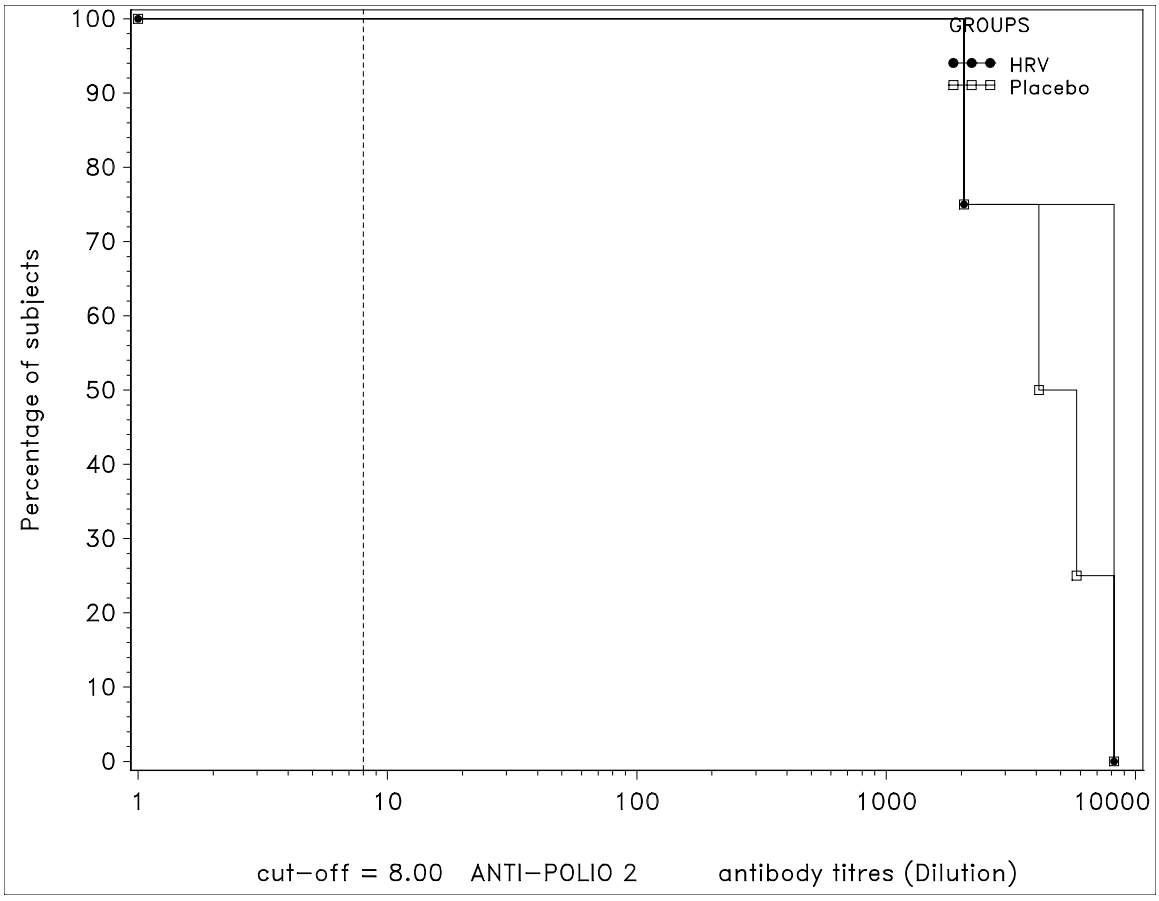
Data source = Appendix table IIIA

Supplement 139 Reverse cumulative curves for anti-Polio1 antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



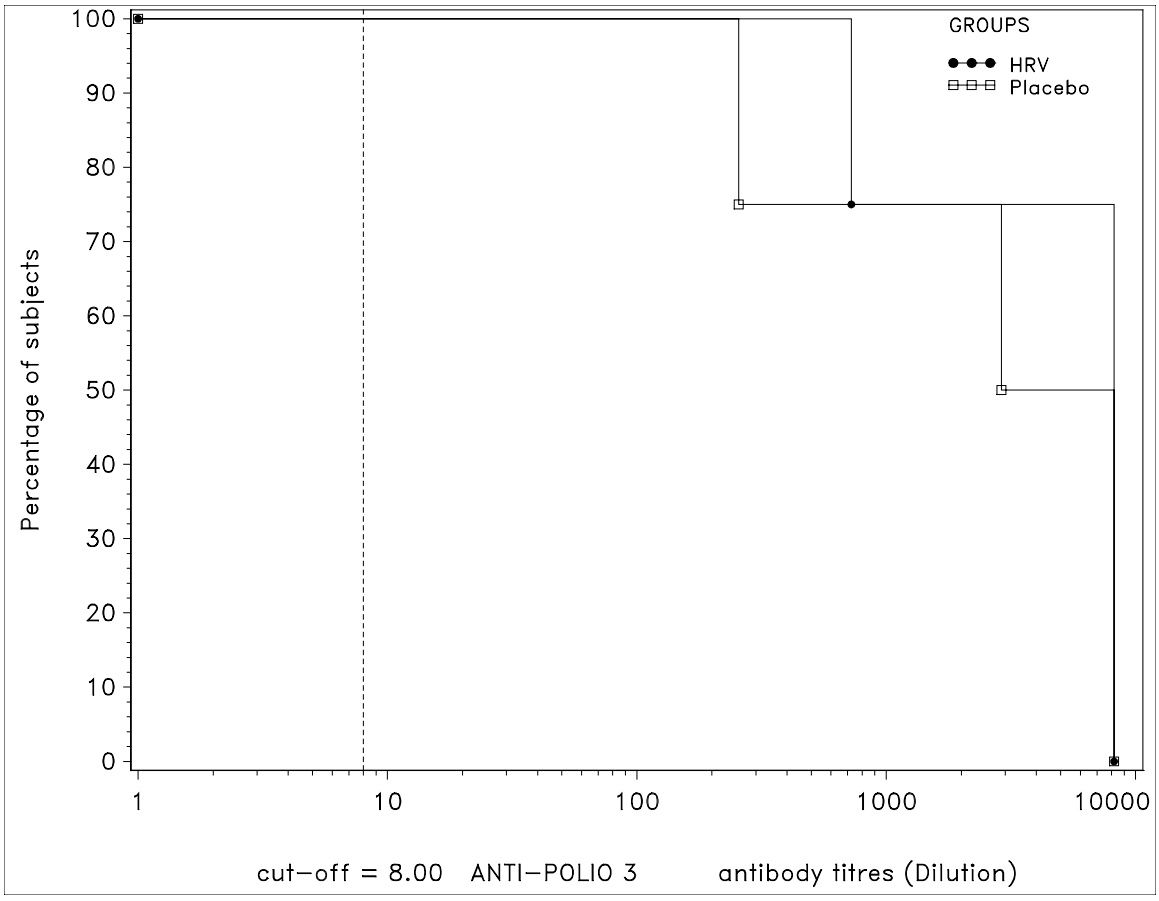
Data source = Appendix table IIIA

Supplement 140 Reverse cumulative curves for anti-Polio2 antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



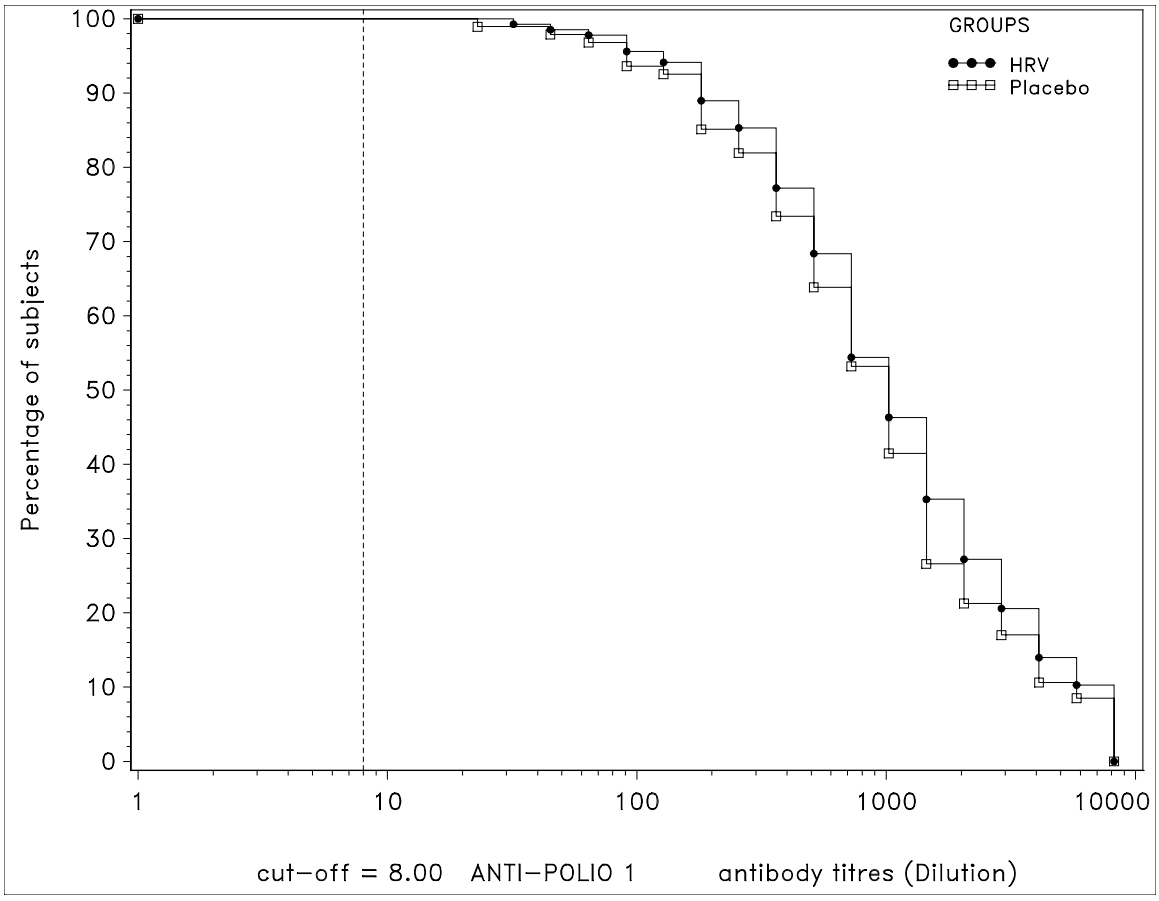
Data source = Appendix table IIIA

Supplement 141 Reverse cumulative curves for anti-Polio3 antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



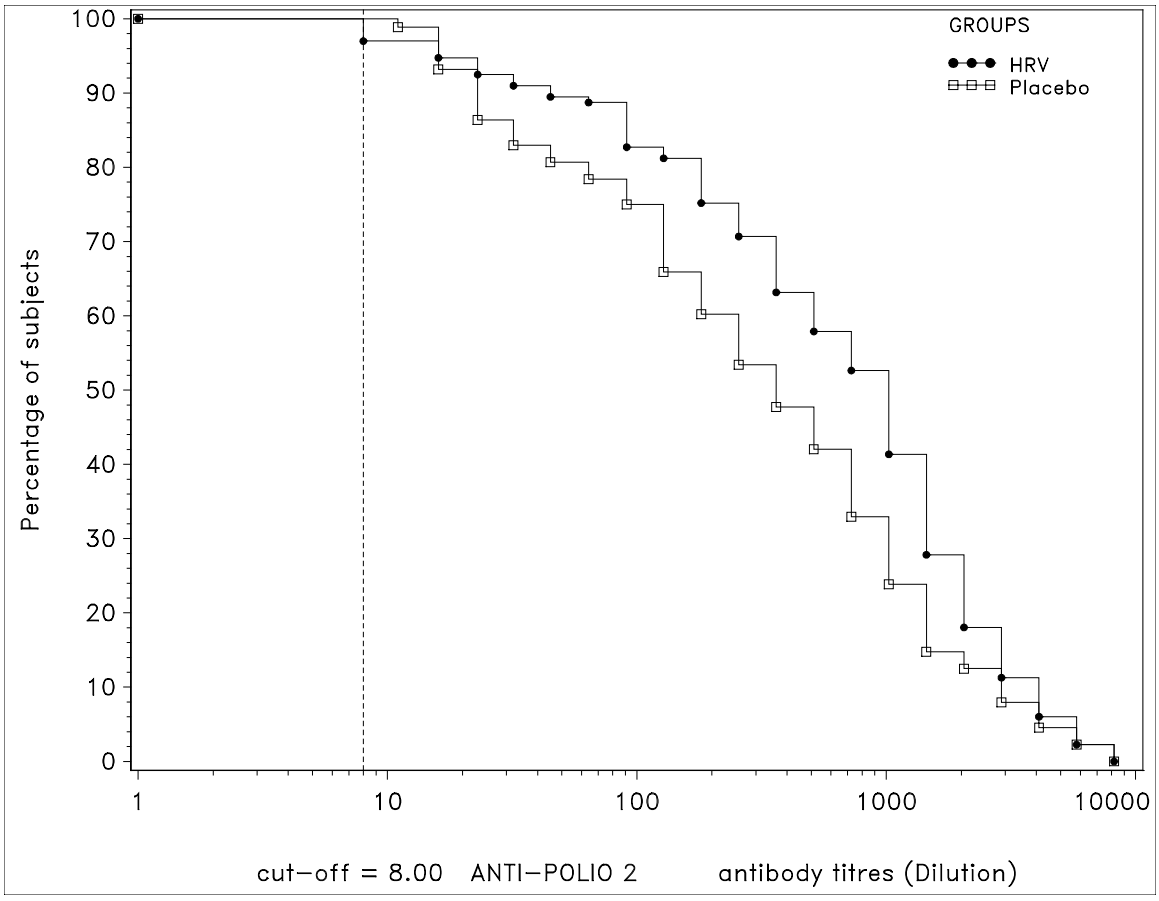
Data source = Appendix table IIIA

Supplement 142 Reverse cumulative curves for anti-Polio1 antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



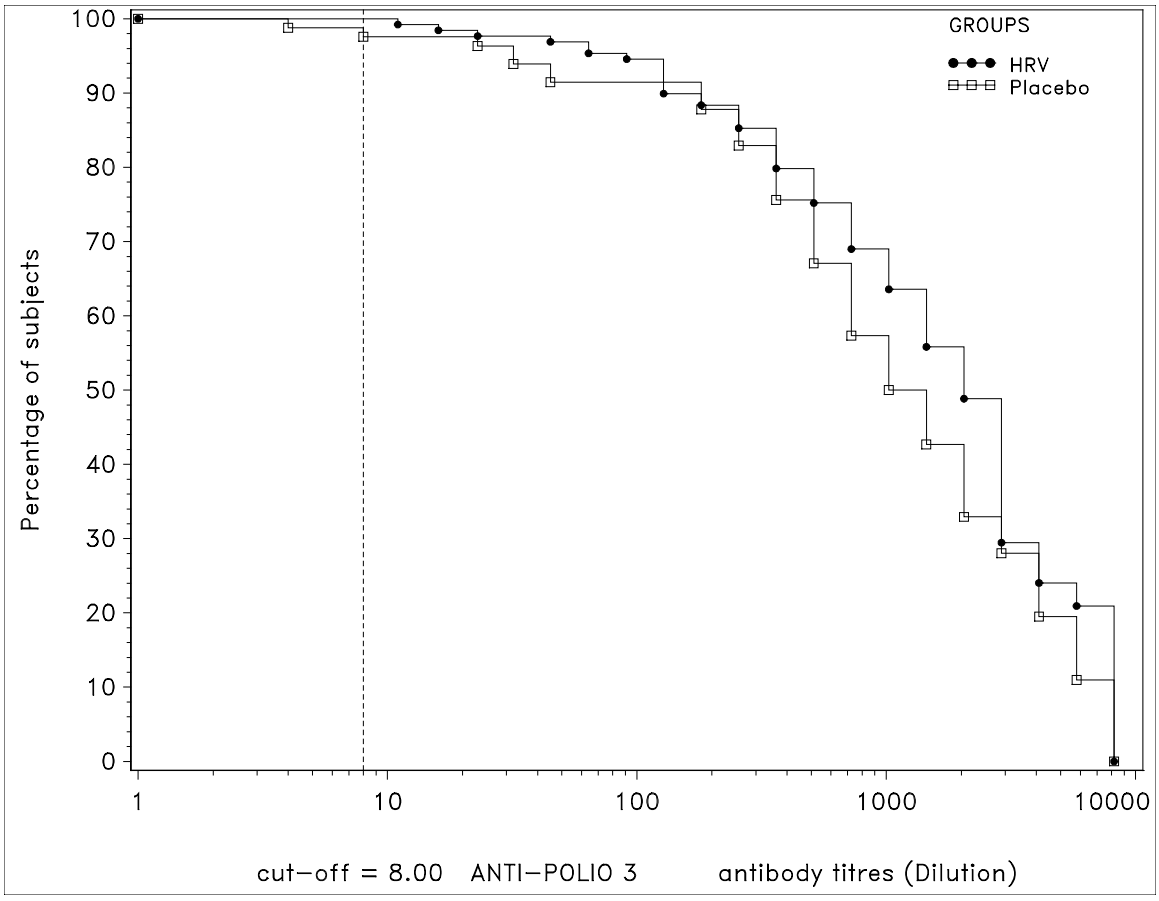
Data source = Appendix table IIIA

Supplement 143 Reverse cumulative curves for anti-Polio2 antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



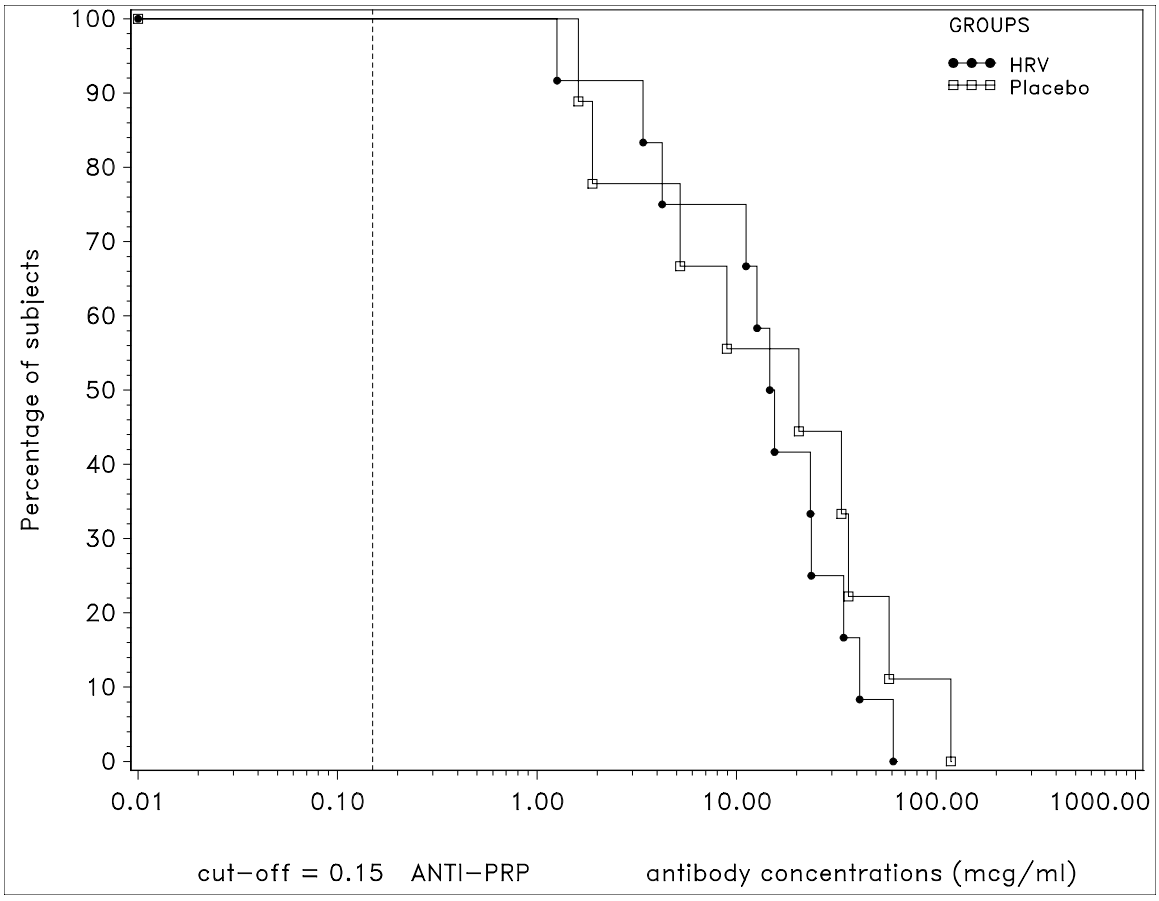
Data source = Appendix table IIIA

Supplement 144 Reverse cumulative curves for anti-Polio3 antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



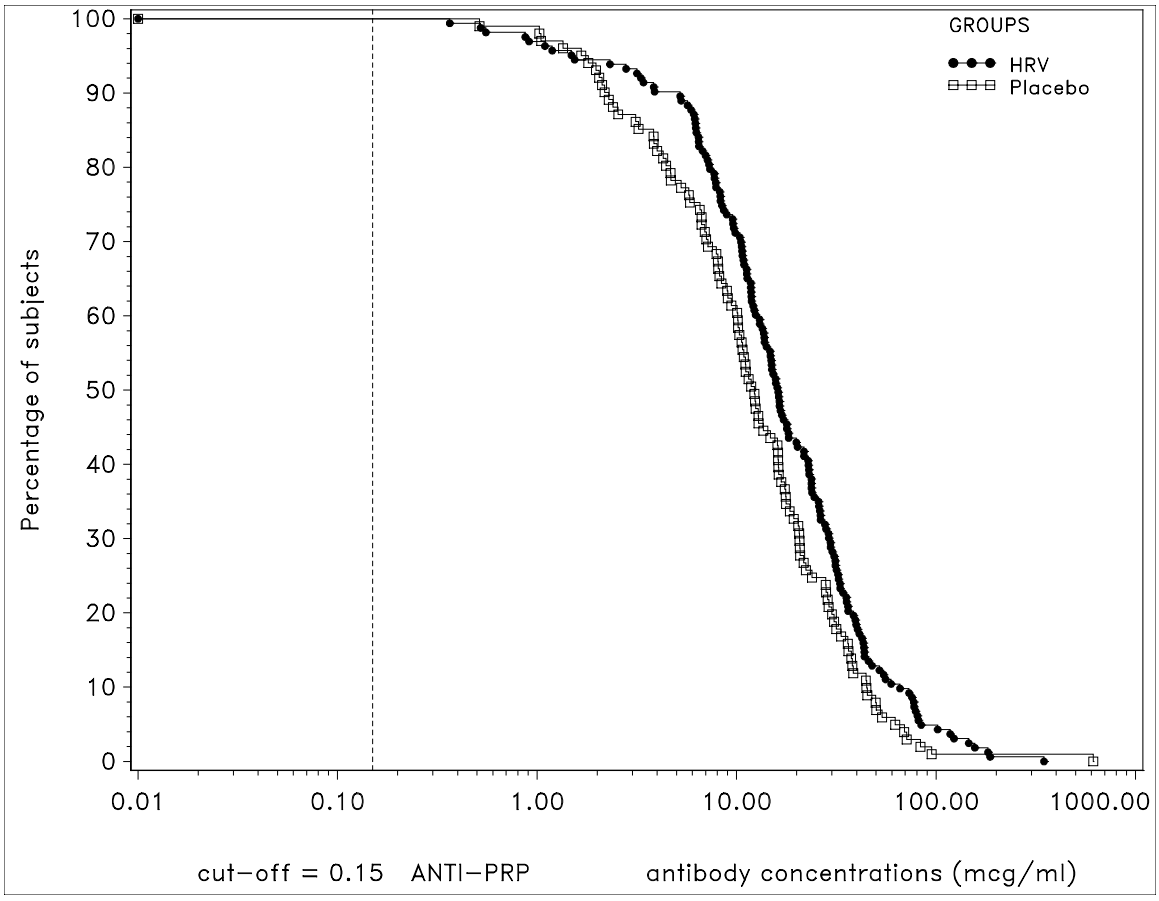
Data source = Appendix table IIIA

Supplement 145 Reverse cumulative curves for anti-PRP antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Italy – ATP cohort for immunogenicity



Data source = Appendix table IIIA

Supplement 146 Reverse cumulative curves for anti-PRP antibody concentrations at post dose 3 (Visit 5/6) of routine childhood vaccination – Finland – ATP cohort for immunogenicity



Data source = Appendix table IIIA

Supplement 147 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PRP concentration greater than or equal to 0.15 UGR/ML – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PRP concentration ≥ 0.15 UGR/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 148 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PRP concentration greater than or equal to 1.0 UGR/ML – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PRP concentration ≥ 1 UGR/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 149 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Diphtheria – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Diphtheria concentration ≥ 0.1 IU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 150 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/ 6) between placebo and HRV groups, for anti-Tetanus – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Tetanus concentration ≥ 0.1 IU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 151 Difference in seropositivity rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PT – Italy – ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PT concentration ≥ 5 EL.U/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 152 Difference in seropositivity rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-FHA – Italy – ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-FHA concentration ≥ 5 EL.U/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 153 Difference in seropositivity rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PRN – Italy – ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	9	100	HRV	12	100	Placebo - HRV	0.00	-29.91	24.25

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PRN concentration ≥ 5 EL.U/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 154 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-HBS – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	8	87.5	HRV	12	100	Placebo - HRV	-12.50	-47.09	13.68

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-HBS concentration ≥ 10 MIU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 155 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Polio 1 – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	4	100	HRV	3	100	Placebo - HRV	0.00	-48.99	56.15

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Polio 1 titre ≥ 8 ED_{50}
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 156 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Polio 2 – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	4	100	HRV	4	100	Placebo - HRV	0.00	-48.99	48.99

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Polio 2 titre ≥ 8 ED50
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 157 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Polio 3 – Italy – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	4	100	HRV	4	100	Placebo - HRV	0.00	-48.99	48.99

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Polio 3 titre ≥ 8 ED_{50}
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 158 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PRP concentration greater than or equal to 0.15 UGR/ML – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	163	100	Placebo - HRV	0.00	-3.66	2.30

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PRP concentration ≥ 0.15 UGR/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 159 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PRP concentration greater than or equal to 1.0 UGR/ML – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	99.0	HRV	163	96.9	Placebo - HRV	2.08	-2.55	6.15

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PRP concentration ≥ 1 UGR/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 160 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Diphtheria – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	164	99.4	Placebo - HRV	0.61	-3.06	3.37

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Diphtheria concentration ≥ 0.1 IU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 161 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Tetanus – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	164	100	Placebo - HRV	0.00	-3.66	2.29

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Tetanus concentration ≥ 0.1 IU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 162 Difference in seropositivity rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PT – Finland – ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	164	100	Placebo - HRV	0.00	-3.66	2.29

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PT concentration ≥ 5 EL.U/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 163 Difference in seropositivity rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-FHA – Finland – ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	164	100	Placebo - HRV	0.00	-3.66	2.29

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-FHA concentration ≥ 5 EL.U/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 164 Difference in seropositivity rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-PRN – Finland – ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	164	100	Placebo - HRV	0.00	-3.66	2.29

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-PRN concentration ≥ 5 EL.U/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 165 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-HBS – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	101	100	HRV	163	100	Placebo - HRV	0.00	-3.66	2.30

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-HBS concentration ≥ 10 MIU/ML
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 166 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Polio 1 – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	94	100	HRV	136	100	Placebo - HRV	0.00	-3.93	2.75

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Polio 1 titre ≥ 8 ED_{50}
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 167 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Polio 2 – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	88	100	HRV	133	100	Placebo - HRV	0.00	-4.18	2.81

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Polio 2 titre ≥ 8 ED_{50}
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 168 Difference in seroprotection rates post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups, for anti-Polio 3 – Finland – ATP cohort for immunogenicity

						Difference in seroprotection rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
Placebo	82	98.8	HRV	129	100	Placebo - HRV	-1.22	-6.59	1.69

Data source = Appendix table IIIA
N = number of subjects with available results
% = percentage of subjects with anti-Polio 3 titre ≥ 8 ED_{50}
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 169 Ratio of anti-PRP antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	9	14.265	HRV	12	13.191	Placebo /HRV	1.08	0.33	3.60

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 170 Ratio of anti-Diphtheria antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	9	7.395	HRV	12	6.738	Placebo /HRV	1.10	0.59	2.05

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 171 Ratio of anti-Tetanus antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	9	6.453	HRV	12	5.766	Placebo /HRV	1.12	0.55	2.28

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 172 Ratio of anti-PT antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	9	79.7	HRV	12	69.7	Placebo /HRV	1.14	0.58	2.25

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 173 Ratio of anti-FHA antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	9	531.3	HRV	12	504.4	Placebo /HRV	1.05	0.61	1.82

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 174 Ratio of anti-PRN antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	9	348.6	HRV	12	285.2	Placebo /HRV	1.22	0.65	2.28

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 175 Ratio of anti-HBS antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	8	2185.8	HRV	12	4030.4	Placebo /HRV	0.54	0.09	3.42

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 176 Ratio of anti-Polio 1 antibody GMTs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMT ratio			
								95% CI	
Group	N	GMT	Group	N	GMT	Ratio order	Value	LL	UL
Placebo	4	3158.4	HRV	3	6502.0	Placebo /HRV	0.49	0.14	1.73

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 177 Ratio of anti-Polio 2 antibody GMTs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMT ratio			
								95% CI	
Group	N	GMT	Group	N	GMT	Ratio order	Value	LL	UL
Placebo	4	4466.8	HRV	4	5792.6	Placebo /HRV	0.77	0.25	2.35

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 178 Ratio of anti-Polio 3 antibody GMTs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Italy – ATP cohort for immunogenicity

						GMT ratio			
								95% CI	
Group	N	GMT	Group	N	GMT	Ratio order	Value	LL	UL
Placebo	4	2655.9	HRV	4	4466.6	Placebo /HRV	0.59	0.05	7.18

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 179 Ratio of anti-PRP antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	11.752	HRV	163	16.051	Placebo /HRV	0.73	0.55	0.98

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 180 Ratio of anti-Diphtheria antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	2.493	HRV	164	2.809	Placebo /HRV	0.89	0.71	1.11

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 181 Ratio of anti-Tetanus antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	4.976	HRV	164	5.583	Placebo /HRV	0.89	0.76	1.05

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 182 Ratio of anti-PT antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	81.7	HRV	164	96.1	Placebo /HRV	0.85	0.74	0.98

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 183 Ratio of anti-FHA antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	476.1	HRV	164	551.3	Placebo /HRV	0.86	0.74	1.00

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 184 Ratio of anti-PRN antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	303.3	HRV	164	307.7	Placebo /HRV	0.99	0.82	1.18

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 185 Ratio of anti-HBS antibody GMCs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
Placebo	101	5577.3	HRV	163	6638.9	Placebo /HRV	0.84	0.62	1.15

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 186 Ratio of anti-Polio 1 antibody GMTs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMT ratio			
								95% CI	
Group	N	GMT	Group	N	GMT	Ratio order	Value	LL	UL
Placebo	94	896.9	HRV	136	1072.1	Placebo /HRV	0.84	0.60	1.17

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 187 Ratio of anti-Polio 2 antibody GMTs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMT ratio			
								95% CI	
Group	N	GMT	Group	N	GMT	Ratio order	Value	LL	UL
Placebo	88	319.4	HRV	133	589.7	Placebo /HRV	0.54	0.34	0.86

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 188 Ratio of anti-Polio 3 antibody GMTs, post dose 3 of routine childhood vaccination (Visit 5/6) between placebo and HRV groups – Finland – ATP cohort for immunogenicity

						GMT ratio			
								95% CI	
Group	N	GMT	Group	N	GMT	Ratio order	Value	LL	UL
Placebo	82	1028.4	HRV	129	1499.4	Placebo /HRV	0.69	0.44	1.06

Data source = Appendix table IIIA
N = number of subjects with available results
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Supplement 189 Seroprotection rates and GMCs for anti-PRP antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.15 UGR/ML				≥ 1 UGR/ML				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	HRV	PII(M3)	15	13	86.7	59.5	98.3	10	66.7	38.4	88.2	1.924	0.652	5.676
		PIII(M9)	14	14	100	76.8	100	14	100	76.8	100	13.343	7.259	24.524
	Placebo	PII(M3)	10	9	90.0	55.5	99.7	5	50.0	18.7	81.3	2.298	0.486	10.861
		PIII(M9)	10	10	100	69.2	100	10	100	69.2	100	15.097	5.404	42.174

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 190 Seroprotection rates and GMCs for anti-Diphtheria and anti-Tetanus antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Diphtheria	HRV	PII(M3)	15	15	100	78.2	100	2.086	1.353	3.217
		PIII(M9)	14	14	100	76.8	100	6.492	4.353	9.682
	Placebo	PII(M3)	10	10	100	69.2	100	2.943	2.085	4.153
		PIII(M9)	10	10	100	69.2	100	7.360	4.795	11.297
anti-Tetanus	HRV	PII(M3)	15	15	100	78.2	100	2.412	1.568	3.711
		PIII(M9)	14	14	100	76.8	100	6.390	4.219	9.676
	Placebo	PII(M3)	10	10	100	69.2	100	2.895	1.543	5.430
		PIII(M9)	10	10	100	69.2	100	6.298	3.573	11.101

Data source = Appendix table IIIA
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 191 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 5 EL.U/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-PT	HRV	PII(M3)	15	15	100	78.2	100	49.9	28.9	86.3
		PIII(M9)	14	14	100	76.8	100	74.0	44.8	122.3
	Placebo	PII(M3)	9	9	100	66.4	100	42.3	27.9	64.2
		PIII(M9)	10	10	100	69.2	100	78.8	64.0	97.0
anti-FHA	HRV	PII(M3)	15	15	100	78.2	100	229.4	154.0	341.6
		PIII(M9)	14	14	100	76.8	100	500.8	339.8	738.3
	Placebo	PII(M3)	10	10	100	69.2	100	149.5	102.4	218.2
		PIII(M9)	10	10	100	69.2	100	495.8	364.5	674.2
anti-PRN	HRV	PII(M3)	15	15	100	78.2	100	121.2	65.2	225.5
		PIII(M9)	14	14	100	76.8	100	310.7	201.2	479.7
	Placebo	PII(M3)	10	10	100	69.2	100	163.1	117.6	226.1
		PIII(M9)	10	10	100	69.2	100	327.0	225.0	475.2

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 192 Seroprotection rates and GMTs for anti-Polio 1, anti-Polio 2 and anti-Polio 3 antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy - Total vaccinated cohort for .the reactogenicity and immunogenicity subset

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1	HRV	PII(M3)	6	6	100	54.1	100	456.1	241.2	862.3
		PIII(M9)	5	5	100	47.8	100	3326.9	928.1	11925.2
	Placebo	PII(M3)	5	5	100	47.8	100	337.8	115.7	986.2
		PIII(M9)	4	4	100	39.8	100	3158.4	929.8	10728.8
anti-Polio 2	HRV	PII(M3)	5	5	100	47.8	100	181.0	20.2	1624.2
		PIII(M9)	6	6	100	54.1	100	4597.6	1748.4	12090.1
	Placebo	PII(M3)	6	6	100	54.1	100	256.0	153.1	428.2
		PIII(M9)	4	4	100	39.8	100	4466.8	1741.6	11456.0
anti-Polio 3	HRV	PII(M3)	5	4	80.0	28.4	99.5	388.0	11.2	13383.7
		PIII(M9)	6	6	100	54.1	100	4095.9	1296.6	12938.1
	Placebo	PII(M3)	6	6	100	54.1	100	304.4	44.0	2107.4
		PIII(M9)	4	4	100	39.8	100	2655.9	197.0	35804.4

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with titre above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 193 Seroprotection rates and GMCs for anti-HBS antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Italy - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-HBS	HRV	PII(M3)	13	13	100	75.3	100	716.5	325.9	1575.5
		PIII(M9)	14	14	100	76.8	100	3977.0	1937.0	8165.5
	Placebo	PII(M3)	9	8	88.9	51.8	99.7	320.0	82.8	1236.0
		PIII(M9)	9	8	88.9	51.8	99.7	2398.7	362.2	15886.5

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M9) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 194 Seroprotection rates and GMCs for anti-PRP antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.15 UGR/ML				≥ 1 UGR/ML				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP	HRV	PII(M3)	179	174	97.2	93.6	99.1	107	59.8	52.2	67.0	1.827	1.453	2.298
		PIII(M10)	174	174	100	97.9	100	169	97.1	93.4	99.1	16.838	14.145	20.043
	Placebo	PII(M3)	110	101	91.8	85.0	96.2	59	53.6	43.9	63.2	1.375	1.019	1.854
		PIII(M10)	107	107	100	96.6	100	106	99.1	94.9	100	11.951	9.622	14.843

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 195 Seroprotection rates and GMCs for anti-Diphtheria and anti-Tetanus antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 0.1 IU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Diphtheria	HRV	PII(M3)	179	164	91.6	86.6	95.2	0.585	0.487	0.703
		PIII(M10)	175	174	99.4	96.9	100	2.810	2.439	3.239
	Placebo	PII(M3)	110	103	93.6	87.3	97.4	0.554	0.445	0.690
		PIII(M10)	107	107	100	96.6	100	2.548	2.189	2.967
anti-Tetanus	HRV	PII(M3)	179	179	100	98.0	100	1.214	1.058	1.393
		PIII(M10)	175	175	100	97.9	100	5.601	5.087	6.167
	Placebo	PII(M3)	110	110	100	96.7	100	1.353	1.140	1.605
		PIII(M10)	107	107	100	96.6	100	5.017	4.430	5.682

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 196 Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 5 EL.U/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-PT	HRV	PII(M3)	179	179	100	98.0	100	50.4	45.7	55.5
		PIII(M10)	175	175	100	97.9	100	94.5	87.2	102.4
	Placebo	PII(M3)	109	109	100	96.7	100	48.0	42.3	54.3
		PIII(M10)	107	107	100	96.6	100	81.5	72.6	91.4
anti-FHA	HRV	PII(M3)	179	179	100	98.0	100	180.4	162.1	200.7
		PIII(M10)	175	175	100	97.9	100	549.4	503.5	599.5
	Placebo	PII(M3)	110	110	100	96.7	100	173.5	153.2	196.5
		PIII(M10)	107	107	100	96.6	100	476.2	424.4	534.4
anti-PRN	HRV	PII(M3)	178	176	98.9	96.0	99.9	79.4	66.5	94.7
		PIII(M10)	175	175	100	97.9	100	309.8	277.8	345.3
	Placebo	PII(M3)	108	107	99.1	94.9	100	95.2	76.2	118.8
		PIII(M10)	107	107	100	96.6	100	307.7	267.8	353.5

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 197 Seroprotection rates and GMTs for anti-Polio 1, anti-Polio 2 and anti-Polio 3 antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1	HRV	PII(M3)	161	139	86.3	80.0	91.2	44.5	34.4	57.6
		PIII(M10)	146	146	100	97.5	100	1102.2	899.0	1351.4
	Placebo	PII(M3)	103	89	86.4	78.2	92.4	37.3	27.2	51.2
		PIII(M10)	99	99	100	96.3	100	899.8	699.1	1158.0
anti-Polio 2	HRV	PII(M3)	164	101	61.6	53.7	69.1	11.5	9.4	14.1
		PIII(M10)	142	142	100	97.4	100	585.8	445.5	770.4
	Placebo	PII(M3)	102	62	60.8	50.6	70.3	11.9	9.3	15.3
		PIII(M10)	93	93	100	96.1	100	322.8	226.3	460.6
anti-Polio 3	HRV	PII(M3)	162	149	92.0	86.7	95.7	76.7	58.2	101.1
		PIII(M10)	138	138	100	97.4	100	1430.0	1104.1	1852.0
	Placebo	PII(M3)	99	86	86.9	78.6	92.8	51.8	35.7	75.1
		PIII(M10)	86	85	98.8	93.7	100	1066.1	751.3	1513.0

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with titre above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII(M10) = post dose 3 of routine childhood vaccination (Visit 5/6)

Supplement 198 Seroprotection rates and GMCs for anti-HBS antibodies post dose 2 (Visit 3) and 3 (Visit 5/6) of routine childhood vaccination – Finland - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 10 MIU/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-HBS	HRV	PII(M3)	178	174	97.8	94.3	99.4	431.6	349.7	532.6
		PIII(M10)	174	174	100	97.9	100	6637.9	5580.8	7895.2
	Placebo	PII(M3)	110	103	93.6	87.3	97.4	405.2	293.8	558.8
		PIII(M10)	107	107	100	96.6	100	5622.9	4355.5	7259.1

Data source = Appendix table IIIA
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M3) = post dose 2 of routine childhood vaccination (Visit 3)
PIII (M10) = post dose 3 of routine childhood vaccination (Visit 5/ 6)

Supplement 199 AE/SAE reported by subjects who dropped-out due to SAEs from dose 1 of HRV vaccine/Placebo up to visit 7 – Total vaccinated cohort

Group	Subject number	SAE/ AE	Symptom (verbatim)	MedDRA PT (code)	Timing (dose/day)	Rel	Start date	End date	Outcome
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.									

Supplement 200 AE/SAE reported by subjects who dropped-out due to AEs from dose 1 of HRV vaccine/Placebo up to visit 7 – Total vaccinated cohort

Group	Subject number	SAE/ AE	Symptom (verbatim)	MedDRA PT (code)	Timing (dose/day)	Rel	Start date	End date	Outcome
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.									

Supplement 201 Percentage of subjects with SAEs occurring from dose 1 of HRV vaccine/Placebo up to visit 7, classified by MedDRA primary System Organ Class (SOC) – Pooled countries – Total vaccinated cohort

	HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	290	11.0	9.8	12.2	176	13.1	11.3	15.0	-2.10	-4.31	0.01	0.051
Blood and lymphatic system disorders (10005329)	8	0.3	0.1	0.6	1	0.1	0.0	0.4	0.23	-0.13	0.53	0.150
Cardiac disorders (10007541)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Congenital, familial and genetic disorders (10010331)	3	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.03	-0.43	0.21	0.767
Eye disorders (10015919)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Gastrointestinal disorders (10017947)	16	0.6	0.3	1.0	5	0.4	0.1	0.9	0.23	-0.30	0.67	0.334
General disorders and administration site conditions (10018065)	6	0.2	0.1	0.5	2	0.1	0.0	0.5	0.08	-0.33	0.37	0.600
Immune system disorders (10021428)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Infections and infestations (10021881)	226	8.5	7.5	9.7	143	10.6	9.0	12.4	-2.07	-4.09	-0.16	**0.033**
Injury, poisoning and procedural complications (10022117)	22	0.8	0.5	1.3	13	1.0	0.5	1.6	-0.13	-0.87	0.45	0.670
Investigations (10022891)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Metabolism and nutrition disorders (10027433)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Nervous system disorders (10029205)	12	0.5	0.2	0.8	12	0.9	0.5	1.5	-0.44	-1.13	0.07	0.091
Psychiatric disorders (10037175)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
Renal and urinary disorders (10038359)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Reproductive system and breast disorders (10038604)	4	0.2	0.0	0.4	3	0.2	0.0	0.6	-0.07	-0.51	0.21	0.610
Respiratory, thoracic and mediastinal disorders (10038738)	13	0.5	0.3	0.8	9	0.7	0.3	1.3	-0.18	-0.81	0.29	0.476
Skin and subcutaneous tissue disorders (10040785)	3	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.03	-0.43	0.21	0.767

Data source = Appendix table IIC

N=number of subjects having received at least one dose of HRV vaccine/placebo

n (%) = number (percentage) of subjects reporting at least one serious adverse event in the specified SOC category from dose 1 of HRV vaccine/Placebo up to visit 7 (or last study contact if Visit 7 not performed)

At least one symptom = at least one symptom experienced, whatever the MedDRA SOC

95% CI = exact 95% confidence interval

95% CI* = asymptotic standardised 95% confidence interval on the risk difference

L.L. = lower limit, U.L. = upper limit

P-value = results of the comparison between groups of percentage of subjects reporting least one SAE in the specified SOC from dose 1 of HRV vaccine/Placebo up to visit 7, by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 have been used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 202 Percentage of subjects with SAEs occurring from dose 1 of HRV vaccine/Placebo up to visit 7, classified by MedDRA primary System Organ Class (SOC) and Preferred Term (PT) – Pooled countries – Total vaccinated cohort

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		290	11.0	9.8	12.2	176	13.1	11.3	15.0	-2.10	-4.31	0.01	0.051
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Aplasia pure red cell (10002965)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Idiopathic thrombocytopenic purpura (10021245)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Lymphadenitis (10025188)	3	0.1	0.0	0.3	0	0.0	0.0	0.3	0.11	-0.17	0.33	0.216
	Thymus enlargement (10065588)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Cardiac disorders (10007541)	Wolff-parkinson-white syndrome (10048015)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Congenital, familial and genetic disorders (10010331)	Amaurotic familial idiocy (10061888)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Atrioventricular septal defect (10063836)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Cerebral palsy (10008129)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Dermoid cyst (10012522)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Lissencephaly (10048911)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Gastrointestinal disorders (10017947)	Colitis (10009887)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Constipation (10010774)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Diarrhoea (10012735)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Enterocolitis (10014893)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Gastritis (10017853)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Gastrointestinal disorder (10017944)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Gastrooesophageal reflux disease (10017885)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Haematochezia (10018836)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Inguinal hernia (10022016)	3	0.1	0.0	0.3	1	0.1	0.0	0.4	0.04	-0.31	0.27	0.711

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Intussusception (10022863)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Stomatitis (10042128)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Vomiting (10047700)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	6	0.2	0.1	0.5	2	0.1	0.0	0.5	0.08	-0.33	0.37	0.600
Immune system disorders (10021428)	Milk allergy (10027633)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Infections and infestations (10021881)	Acute tonsillitis (10001093)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Arthritis bacterial (10053555)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Bacterial pyelonephritis (10059517)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Bronchiolitis (10006448)	26	1.0	0.6	1.4	18	1.3	0.8	2.1	-0.35	-1.18	0.31	0.313
	Bronchitis (10006451)	8	0.3	0.1	0.6	4	0.3	0.1	0.8	0.01	-0.48	0.35	0.976
	Bronchitis acute (10006452)	8	0.3	0.1	0.6	4	0.3	0.1	0.8	0.01	-0.48	0.35	0.976
	Bronchitis chronic (10006458)	42	1.6	1.1	2.1	23	1.7	1.1	2.5	-0.12	-1.05	0.67	0.779
	Bronchitis viral (10053160)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Bronchopneumonia (10006469)	5	0.2	0.1	0.4	0	0.0	0.0	0.3	0.19	-0.10	0.44	0.110
	Campylobacter gastroenteritis (10007048)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Cellulitis (10007882)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Coxsackie viral infection (10011261)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Ear infection (10014011)	2	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.07	-0.47	0.15	0.492
	Erysipelas (10015145)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Exanthema subitum (10015586)	5	0.2	0.1	0.4	5	0.4	0.1	0.9	-0.18	-0.69	0.14	0.277
	Febrile infection (10051998)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Gastroenteritis (10017888)	21	0.8	0.5	1.2	24	1.8	1.1	2.6	-0.99	-1.89	-0.28	**0.005**
	Gastroenteritis adenovirus (10017889)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Gastroenteritis bacterial (10061166)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Gastroenteritis clostridial (10017898)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Gastroenteritis rotavirus (10017913)	1	0.0	0.0	0.2	26	1.9	1.3	2.8	-1.89	-2.78	-1.27	**0.000**
	Gastroenteritis salmonella (10017914)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Herpangina (10019936)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Herpetic gingivostomatitis (10019996)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Infection (10021789)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Influenza (10022000)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Laryngitis (10023874)	22	0.8	0.5	1.3	15	1.1	0.6	1.8	-0.28	-1.05	0.33	0.380
	Laryngotracheitis (10023882)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Laryngotracheo bronchitis (10023884)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Lobar pneumonia (10024738)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Lower respiratory tract infection (10024968)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Lung infection (10061229)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Measles (10027011)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Meningitis (10027199)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Nasopharyngitis (10028810)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Orchitis (10031064)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Otitis media (10033078)	20	0.8	0.5	1.2	4	0.3	0.1	0.8	0.46	-0.06	0.92	0.076
	Otitis media acute (10033079)	1	0.0	0.0	0.2	1	0.1	0.0	0.4	-0.04	-0.38	0.15	0.627
	Perianal abscess (10034447)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Periorbital cellulitis (10057182)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pertussis (10034738)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pharyngitis (10034835)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Pneumococcal bacteraemia	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	(10058859)												
	Pneumococcal sepsis (10054047)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pneumonia (10035664)	24	0.9	0.6	1.3	4	0.3	0.1	0.8	0.61	0.08	1.10	**0.029**
	Pneumonia respiratory syncytial viral (10035732)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Pneumonia viral (10035737)	1	0.0	0.0	0.2	2	0.1	0.0	0.5	-0.11	-0.50	0.09	0.228
	Pyelonephritis (10037596)	10	0.4	0.2	0.7	8	0.6	0.3	1.2	-0.22	-0.82	0.21	0.336
	Pyelonephritis acute (10037597)	9	0.3	0.2	0.6	5	0.4	0.1	0.9	-0.03	-0.55	0.34	0.876
	Respiratory syncytial virus infection (10061603)	4	0.2	0.0	0.4	2	0.1	0.0	0.5	0.00	-0.40	0.27	0.983
	Respiratory tract infection (10062352)	5	0.2	0.1	0.4	1	0.1	0.0	0.4	0.11	-0.24	0.38	0.376
	Sepsis (10040047)	3	0.1	0.0	0.3	2	0.1	0.0	0.5	-0.03	-0.43	0.21	0.767
	Skin infection (10040872)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Streptococcal bacteraemia (10051018)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Streptococcal sepsis (10048960)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Subcutaneous abscess (10042343)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Superinfection (10042566)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Tonsillitis (10044008)	1	0.0	0.0	0.2	3	0.2	0.0	0.6	-0.18	-0.62	0.03	0.081
	Upper respiratory tract infection (10046306)	5	0.2	0.1	0.4	1	0.1	0.0	0.4	0.11	-0.24	0.38	0.376
	Urinary tract infection (10046571)	4	0.2	0.0	0.4	4	0.3	0.1	0.8	-0.15	-0.62	0.15	0.331
	Varicella (10046980)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Viral infection (10047461)	5	0.2	0.1	0.4	2	0.1	0.0	0.5	0.04	-0.36	0.32	0.772
Injury, poisoning and procedural complications (10022117)	Accidental exposure (10000378)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Accidental overdose (10000381)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Animal bite (10002515)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Clavicle fracture (10009245)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Concussion (10010254)	4	0.2	0.0	0.4	3	0.2	0.0	0.6	-0.07	-0.51	0.21	0.610

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Contusion (10050584)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Drug toxicity (10013746)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Fall (10016173)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Femur fracture (10016454)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Foreign body trauma (10017051)	4	0.2	0.0	0.4	0	0.0	0.0	0.3	0.15	-0.13	0.39	0.153
	Head injury (10019196)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	**0.047**
	Limb injury (10061225)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Poisoning (10061355)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Skin laceration (10058818)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Skull fracture (10061365)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Thermal burn (10053615)	4	0.2	0.0	0.4	5	0.4	0.1	0.9	-0.22	-0.72	0.09	0.166
	Tibia fracture (10043827)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Investigations (10022891)	Medical observation (10053047)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Metabolism and nutrition disorders (10027433)	Cow's milk intolerance (10011241)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Dehydration (10012174)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Diabetes mellitus (10012601)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Hypoglycaemia (10020993)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Primitive neuroectodermal tumour (10057846)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Nervous system disorders (10029205)	Balance disorder (10049848)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Convulsion (10010904)	1	0.0	0.0	0.2	3	0.2	0.0	0.6	-0.18	-0.62	0.03	0.081
	Epilepsy (10015037)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Febrile convulsion (10016284)	7	0.3	0.1	0.5	5	0.4	0.1	0.9	-0.11	-0.62	0.24	0.561
	Hypotonia (10021118)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Infantile spasms (10021750)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Loss of consciousness (10024855)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Myoclonus (10028622)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Partial seizures (10061334)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161

		HRV N = 2646				Placebo N = 1348				Risk Difference (HRV minus Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Syncope (10042772)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Psychiatric disorders (10037175)	Breath holding (10006322)	2	0.1	0.0	0.3	0	0.0	0.0	0.3	0.08	-0.21	0.28	0.313
	Sleep disorder (10040984)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Renal and urinary disorders (10038359)	Haematuria (10018867)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
Reproductive system and breast disorders (10038604)	Balanitis (10004073)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Phimosis (10034878)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Scrotal oedema (10039755)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Testicular appendage torsion (10050476)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Testicular cyst (10048872)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Testicular torsion (10043356)	0	0.0	0.0	0.1	2	0.1	0.0	0.5	-0.15	-0.54	-0.00	**0.047**
Respiratory, thoracic and mediastinal disorders (10038738)	Adenoidal hypertrophy (10001229)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Apnoea (10002974)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Aspiration (10003504)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Asthma (10003553)	8	0.3	0.1	0.6	6	0.4	0.2	1.0	-0.14	-0.69	0.24	0.470
	Atelectasis (10003598)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
	Bronchospasm (10006482)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Dyspnoea (10013968)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Pneumonitis (10035742)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Tonsillar disorder (10053477)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161
Skin and subcutaneous tissue disorders (10040785)	Dermatitis allergic (10012434)	1	0.0	0.0	0.2	0	0.0	0.0	0.3	0.04	-0.25	0.21	0.475
	Dermatitis atopic (10012438)	2	0.1	0.0	0.3	1	0.1	0.0	0.4	0.00	-0.35	0.21	0.988
	Rash (10037844)	0	0.0	0.0	0.1	1	0.1	0.0	0.4	-0.07	-0.42	0.07	0.161

Data source = Appendix table IIC
N=number of subjects having received at least one dose of HRV vaccine/placebo
n (%) = number (percentage) of subjects reporting at least one serious adverse event in the specified PT category from dose 1 of HRV vaccine/Placebo up to visit 7 (or last study contact if Visit 7 not performed)
At least one symptom = at least one symptom experienced, whatever the MedDRA PT
95% CI = exact 95% confidence interval
95% CI* = asymptotic standardised 95% confidence interval on the risk difference
L.L. = lower limit, U.L. = upper limit
P-value = results of comparison between groups of percentage of subjects reporting least one SAE in the specified PT from dose 1 of HRV vaccine/Placebo up to visit 7, by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-values less than 0.05 have been used as an aid to highlight potential differences worth further attention. However care must be taken when interpreting putative statistically significant findings since there were no adjustments for multiplicity and clinical significance must be taken into account).

Supplement 203 Percentage of doses and of subjects having at least one concomitant medication reported during the study period, by type – Pooled countries – Total vaccinated cohort

	HRV					Placebo				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1										
Any	2646	1002	37.9	36.0	39.7	1348	450	33.4	30.9	36.0
Any antipyretic	2646	749	28.3	26.6	30.1	1348	327	24.3	22.0	26.6
Prophylactic antipyretic	2646	77	2.9	2.3	3.6	1348	31	2.3	1.6	3.2
Any antibiotic	2646	143	5.4	4.6	6.3	1348	61	4.5	3.5	5.8
Dose 2										
Any	2621	1290	49.2	47.3	51.2	1338	665	49.7	47.0	52.4
Any antipyretic	2621	898	34.3	32.4	36.1	1338	459	34.3	31.8	36.9
Prophylactic antipyretic	2621	40	1.5	1.1	2.1	1338	25	1.9	1.2	2.7
Any antibiotic	2621	306	11.7	10.5	13.0	1338	149	11.1	9.5	12.9
Overall/dose										
Any	5267	2292	43.5	42.2	44.9	2686	1115	41.5	39.6	43.4
Any antipyretic	5267	1647	31.3	30.0	32.5	2686	786	29.3	27.5	31.0
Prophylactic antipyretic	5267	117	2.2	1.8	2.7	2686	56	2.1	1.6	2.7
Any antibiotic	5267	449	8.5	7.8	9.3	2686	210	7.8	6.8	8.9
Overall/subject										
Any	2646	1643	62.1	60.2	63.9	1348	798	59.2	56.5	61.8
Any antipyretic	2646	1187	44.9	43.0	46.8	1348	568	42.1	39.5	44.8
Prophylactic antipyretic	2646	94	3.6	2.9	4.3	1348	43	3.2	2.3	4.3
Any antibiotic	2646	407	15.4	14.0	16.8	1348	196	14.5	12.7	16.5

For each dose: N = number of subjects having received the considered dose of HRV vaccine/ Placebo
n (%) = number(percentage) of subjects who started taking the specified concomitant medication at least once after the considered HRV vaccine/Placebo dose, during the study period
For overall/dose: N = total number of HRV vaccine/ Placebo doses administered
n (%) = number(percentage) of HRV vaccine/ Placebo doses with at least one specified concomitant medication, during the study period
For overall/subject: N= total number of subjects having received at least one dose of HRV vaccine/Placebo
n (%) = total number(percentage) of subject who started taking the specified concomitant medication at least once after any HRV vaccine/Placebo doses, during the study period
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Data source = Appendix table IIDi

Appendix 1 Individual Listings

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****.*

Appendix 3 Study Information

Appendix 3A Sponsor Information

Sponsor Information for the Czech Republic

eTrack study number 102247
eTrack abbreviated title rota-036 - Europe

1. (Principal) Investigator

Ass. Prof., [redacted] M.D., PhD.
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2. Medical Monitor

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Fax: [redacted]
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3. Local Study Monitor

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4. Local Contact for Reporting of a Serious Adverse Event

Safety Team
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6. Study Centres

Multiple sites.

Sponsor Information for Finland

eTrack study number 102247
eTrack abbreviated title rota-036 - Europe

1. (Principal) Investigator

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2. Medical Monitor

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6. Study Centres

Multiple sites.
Central, co-ordinating unit:
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Finland

Sponsor Information for France

eTrack study number 102247
eTrack abbreviated title rota-036 - Europe

1. (Principal) Investigator

2. Medical Monitor

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After January 2005

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3. Local Monitor

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5. Local Contact for Emergency Code Break

6. Study Centres
Multiple sites

Sponsor Information for Germany

eTrack study number 102247
eTrack abbreviated title rota-036 - Europe

1. (Principal) Investigator

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4. Study Monitor

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7. Study Centres

Multiple sites

Sponsor Information for Italy

eTrack study number 102247
eTrack abbreviated title rota-036 - Europe

1. (Principal) Investigator

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5. Study Contact for Emergency Code Break

6. Study Centres

Multiple sites.

Sponsor Information for Spain

eTrack study number 102247
eTrack abbreviated title rota-036 - Europe

1. Principal Investigators

2. Medical Monitor

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5. Local Contact for Emergency Code Break

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28760 Tres Cantos (Madrid), Spain
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Fax.: [redacted]

6. Study Centres

Multiple sites.

Appendix 3B Protocol and Protocol Amendments

GlaxoSmithKline Biologicals
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B-1330 Rixensart Belgium

Study vaccine(s)	GSK Biologicals' live attenuated oral human rotavirus (HRV) vaccine.
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Date of approval	Final 11 June 2004 **Amendment 1: 07 June 2005**
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	[redacted] Director [redacted] Biostatistician [redacted] ***Clinical Development Manager*** **(Amendment 1: 07 June 2005)** [redacted] Central Study Coordinator

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Sponsor signatory:	
	[redacted] ***Director*** **(Amendment 1: 07 June 2005)**

Investigator Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine) and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: _____

Investigator Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
Date of approval	Final 11 June 2004
	Amendment 1: 07 June 2005
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine) and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: _____

[For Germany only]

"**Leiter der klinischen Prüfung" (LKP) name:** _____

Synopsis

Title A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Indication/Study population Two-dose immunization according to 0, 1 or 2-month schedule against rotavirus disease in healthy infants aged 6 to 14 weeks at the time of the first dose.

Rationale Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) in young children in both developed and developing countries. The heavy global health burden prompted the development of vaccines against rotavirus illness. GlaxoSmithKline (GSK) Biologicals therefore aims to develop a safe and efficacious rotavirus vaccine that can be used with routine childhood vaccines to meet this health need.

GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. This vaccine has been tested extensively in Phase I, II and III trials and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.

This study will evaluate the efficacy, safety and immunogenicity of GSK Biologicals' HRV study vaccine at the selected optimum dose in healthy infants and will provide specific data in the European setting. The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis during the period starting 2 weeks after the second dose of study vaccination and ending at Visit 5 (mid-June to end-July 2005). Efficacy evaluation will continue during a second efficacy follow-up period ending at Visit 7 (mid-June to end-July 2006). The total study length will thus be approximately 22 months and will not exceed a total of maximum of 24 months.

This study will also assess the immune response to concomitantly administered childhood vaccinations. The co-administration of routine childhood vaccines with the HRV vaccine has been studied in other trials and no interference on immunogenicity was found. However, co-administration of some specific combination childhood vaccines in use in Europe has not been tested yet. This study will therefore evaluate concomitant administration of specific childhood vaccines currently recommended in Europe. Subjects in each participating country will receive combination childhood vaccines that comply with the current local national Plan of Immunization schedule concomitantly with each HRV vaccine or placebo dose.

The study will further evaluate factors that are useful in understanding

the epidemiology of rotavirus infections in a European context.

Objectives **Primary**

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Definitions

GE: Diarrhea with or without vomiting.

RV GE for efficacy analysis: An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.

Severe RV GE: An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system [Ruuska, 1990]). Additional alternative scoring systems may be evaluated (exploratory analyses, see Sections 8.12 and 10.6.2).

Efficacy follow-up period: All subjects will be followed over two efficacy follow-up periods. Study enrolment will start September 2004. The first efficacy follow-up period will begin 2 weeks after Dose 2 of study vaccination and end at Visit 5 (mid-June to end-July 2005). The second efficacy follow-up period will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006) covering approximately 12 months.

Also, refer to Glossary of Terms for definition of terms used.

Secondary

Efficacy

First efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations

against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- To assess vaccine efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season.

Second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice,

visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Combined efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in the immunogenicity and reactogenicity subset, N=1800)

- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccines (depending on the vaccination schedule in respective participating countries, Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® or Meningitec® vaccines will be co-administered; in case of problems with availability of Meningetec® a similar alternative that is approved in Spain can be considered).

Safety and reactogenicity

- In the immunogenicity and reactogenicity subset (N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (31 days after each dose) and serious adverse events during the entire course of the study.

Study design

- Experimental design: Double-blind, randomized, placebo-controlled, multi-country and multi-center study with two parallel groups.
- Control: Placebo (The placebo consist of all components of the study vaccine i.e. excipients and buffer, but no rotavirus particles).
- Blinding: Double-blind. See section 6.5 for details of blinding procedure.
- Treatment allocation: Randomized (2:1 ratio). See section 6.4 for a detailed description of the randomization method.
- Treatment Groups:

  Group HRV vaccine (N=2660): subjects will receive two doses of HRV vaccine co-administered with specific childhood vaccines

  Group Placebo (N=1330): subjects will receive two doses of placebo co-administered with specific childhood vaccines
- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months
  Finland: 3, 5, ***11***-12 months **(Amendment 1: 07 June 2005)**
  France and Germany: 2, 3, 4 months.
  Italy: 3, 5, 11 months
  Spain: 2, 4, 6 months

- Vaccination schedule: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.
- Concomitant vaccinations:

➢ In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing

diphtheria and tetanus toxoids and acellular pertussis (DTPa), *Haemophilus influenzae* type b (Hib), Hepatitis B vaccine (HBV), and inactivated poliovirus vaccine (IPV)] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

- In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

  - Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
  - Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

  Thereafter, routine vaccinations will be given as per the recommended respective national Plan of Immunisation schedule of each country.

- Study visits: All subjects will have five study visits (Visits 1, 2, 3, 5 and 7). Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** have ***if necessary*** one additional visit (Visit 6). **(Amendment 1: 07 June 2005)**

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=1800), Dose 1 (HRV vaccine or placebo) and Dose 1 specific childhood vaccines.

  Visit 2 (Month 1 or 2) – Dose 2 (HRV vaccine or placebo), Dose 2 specific childhood vaccines, follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Visit 3 (Month 3 or 4) – Post-vaccination blood sample from a subset of subjects (N=1800), follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and

follow-up for safety.

Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines. The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain, Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). Subjects in the Czech Republic, France and Germany will not require a separate visit since the blood sampling at post Dose 3 of the childhood vaccines coincides with Visit 3. **(Amendment 1: 07 June 2005)**

Visit 4 ("immunogenicity and reactogenicity subset" in Spain only) one month after the third dose of the primary vaccination course at 7 months of age – Post-vaccination blood sample from all subjects in Spain (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 5 (mid-June to end-July 2005) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Visit 6 ("immunogenicity and reactogenicity subset" in Italy and Finland only) one month after the third dose of the primary vaccination course

In Italy: Visit 6 at 12 months of age – Post-vaccination blood sample from all subjects in Italy (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

In Finland: Visit 6 at 13 months of age – Post-vaccination blood sample from a subset of subjects (N=300), follow-up for GE episodes with return of any GE cards and follow-up for

safety (SAEs).

Visit 7 (mid-June to end-July 2006) – Follow-up for GE episodes with return of any GE cards, follow-up for safety (SAEs) and study conclusion.

- Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

  For each GE episode occurring during the study period, a GE diary card should be completed daily until end of the GE symptoms. During each GE episode, a stool sample(s) should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms.

- Specific solicited symptoms occurring during the 8-day follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo will be recorded by parents/guardians of a subset of subjects (N=1800) using diary cards. Unsolicited symptoms occurring within 31 days (Day 0-Day 30) after each study vaccine dose and SAEs during the entire study period will be recorded in all subjects. Parents/guardians will be asked to contact the investigator or his/her delegate in case of SAEs or IS during the study. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as contact through telephone call, SMS using cellular phone, an Independent Calling Centre or other convenient means).

- An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case is reviewed by this committee.

- Duration of the study: Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per

subject, will not exceed a total of maximum of 24 months.

- Data collection: Remote Data Entry (RDE).
- Refer to Appendix C for a summary of the recruitment plan.

Number of subjects

Total target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group).

All enrolled subjects will be followed for efficacy and safety.

Subjects will be enrolled at multiple sites in up to six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain). A target total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.

A subset of 1800 subjects (target 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Secondary endpoints

Efficacy during the first efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first

efficacy follow-up period.

- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season.

Efficacy during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Efficacy during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined

efficacy follow-up period.

- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in a subset of subjects, N=1800)

- Serum rotavirus IgA antibody concentration expressed as GMC at Visit 1 and Visit 3.
- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3.

  Seroconversion is defined as 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) seronegative for rotavirus.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccines at Visit 3 and Visit 4 or Visit 6 (if applicable):
  - Serum concentration/titer expressed as GMC/Ts for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP, anti-HBs, anti-Men C or antibodies to the 7 *Streptococcus pneumoniae* serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-polio type 1 antibody titers ≥ 8
    - anti-polio type 2 antibody titers ≥ 8
    - anti-polio type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml

- anti-HBs antibody concentrations ≥ 10.0 mIU/ml
- *Neisseria meningitidis* C serum bactericidal activity titer ≥ 1/8
- ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥0.3 mcg/ml*** **(Amendment 1: 07 June 2005)**
- antibody concentrations to *Streptococcus pneumoniae* serotypes 4, 9V,14, 18C, 23 F, 6B, 19F ≥ 0.05 mcg/ml

- Seropositivity status:
  - anti-PT antibody concentrations ≥ 5 EL.U/ml
  - anti-FHA antibody concentrations ≥ 5 EL.U/ml
  - anti-PRN antibody concentrations ≥ 5 EL.U/ml

Safety and reactogenicity

- In a subset of subjects (N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccines.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccines, according to the MedDRA classification.
- For all subjects, occurrence of serious adverse events throughout the entire study period.

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List of Abbreviations

AE	Adverse event
ATP	According-to-protocol
CCID50	median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CI	Confidence Interval
CRA	Clinical Research Associate
CSC	Central Study Coordinator
D	Diphtheria toxoid
DCSI	Development Core Safety Information
DMEM	Dulbecco's Modified Eagle Medium
DTPa	Diphtheria and tetanus toxoids and acellular pertussis
eCRF	Electronic Case Report Form
ED50	Estimated dose 50%
EISR	Expedited Investigator Safety Report
ELISA	Enzyme Linked ImmunoSorbent Assay
EL.U	Elisa units
EPI	Expanded Program on Immunization
FHA	Filamentous haemagglutinin
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC/T	Geometric Mean Concentration/Titers
GSK	GlaxoSmithKline
HBV	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus

HRV	Human Rotavirus
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPV	Inactivated poliovirus vaccine
IRB	Institutional Review Board
IS	Intussusception
IU	International Units
MedDRA	Medical Dictionary for Regulatory Activities
PID	Patient Identification Number
PMS	Post marketing surveillance
PRN	Pertactin
PRP	Polyribosyl ribitol phosphate
PT	Pertussis toxoid
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SMS	Short Message Service
SOP	Standard Operating Procedures
T	Tetanus toxoid
U	Units

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Blinding:	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. Partially blind is to be used for study designs with different blinding levels between different groups, e.g. double blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring proper conduct of a clinical study.
Completed:	Subject who complete the final study visit foreseen in the protocol.
Diarrhea:	Passage of three or more looser than normal stools within a day.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.4 and 10.4 for details on criteria for evaluability).
First efficacy follow-up period:	Period starting from two weeks after Dose 2 of study vaccine or placebo and ending at Visit 5 (mid-June to end-July 2005).
Gastroenteritis:	Diarrhea with or without vomiting
IDMC:	Independent Data Monitoring Committee. The IDMC is responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in

	order to reduce bias of selection
Rotavirus gastroenteritis for efficacy analysis:	An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.
Rotavirus season:	The rotavirus epidemic season is expected from beginning of December to end of May in Europe.
Second efficacy follow-up period:	Period starting on the day after Visit 5 and ending at Visit 7 (mid-June to end-July 2006).
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 units (U)/milliliter (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) seronegative for rotavirus.
Seronegative:	A subject with antibody concentration below the assay cut-off value.
Seropositive:	A subject with antibody concentration 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 (Vesikari scoring system).
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event:	Adverse events (AEs) to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Study Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or

	placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.
Unsolicited adverse event:	Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1. INTRODUCTION

1.1. Background

Rotavirus (RV) is the most common cause of severe diarrhea and dehydration among young children in both developed and developing countries. Reviews of epidemiological data estimate that, world-wide, RV causes approximately 138 -140 million cases of diarrhea annually accounting for 20% of outpatient or clinic visits for diarrhea, 26% of hospitalizations for diarrhea and a total of 440 000-452 000 deaths in children under 5 years of age annually [Parashar, 2003]. The majority of these deaths occur in Africa, Indian subcontinent and Latin America. Epidemiologic studies have shown that the estimated RV disease burden in different European countries is high [Vesikari, 1999; Koopmans , 1999; Mrukowicz, 1999; Johansen, 1999] and most of this burden is due to RV-associated hospitalization of young children. In Europe, the estimated RV associated hospitalization rates among children under 5 years of age vary from 1 in 33 cases of RV infection in Finland, 1 in 54 in Sweden, 1 in 65 in Poland, 1 in 74 in the Netherlands and 1 in 80 in Spain [Gil, 2004].

The significant global health burden due to RV disease in both developed and developing countries prompted the development of RV vaccines. Prevention by vaccination is considered to be critical for effective control of RV infection since only non-specific symptomatic therapies are available. A variety of approaches to the development of RV vaccines have been undertaken, with live oral attenuated vaccines receiving the most attention. One vaccine, Rotashield®, a tetravalent rhesus human reassortant RV vaccine (RRV-TV), was licensed by Wyeth-Lederle in the United States in 1998 and was granted a marketing authorization for Europe in 1999 but was withdrawn from the market in 1999 due to an increased risk of intussusception (IS) (telescoping of the intestine) shortly after its administration. GlaxoSmithKline (GSK) Biologicals therefore aims to develop a safe and efficacious human rotavirus vaccine to meet this health need. GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old infant with a mild RV diarrhea in Cincinnati, United States. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilized HRV vaccine containing RIX4414 cloned from 89-12 at passage 43 for oral administration after reconstitution with buffer. The parent 89-12 vaccine was well-tolerated, immunogenic and effective in preventing RV GE among vaccinated infants during a trial in the United States [Bernstein, 1998; Bernstein , 1999; Bernstein, 2002].

GSK's RIX4414 candidate HRV differs from Rotashield®, because it is based on a human strain, whereas Rotashield® was based on a rhesus strain. There are major differences in terms of biological properties and clinical symptoms between animal (rhesus) and human RV strains, while only minor differences are expected between the attenuated RIX4414 HRV strain and the wild-type HRV. Wild-type HRV has not been associated with IS in infants. The most powerful evidence refuting a link between wild type HRV infection and IS is the absence of an increase in IS rates during the sharply defined winter RV epidemics that occur in temperate climates [Rennels , 1998]. The

RIX4414 human strain in GSK Biologicals' candidate HRV vaccine is attenuated and the attenuation might further decrease any possible, albeit unlikely, link to IS. Administration of GSK's HRV vaccine candidate does not induce a viral exposure that would otherwise not occur, in contrast with the administration of the rhesus rotavirus vaccine which represents a virus that would not normally infect children. The potential risk for the induction of IS by RIX4414 is being currently studied in large Phase III trials and the results will be available before the first enrolment in this study.

Clinical results of the GSK Biologicals HRV vaccine

GSK Biologicals' HRV vaccine has been tested in Phase I-III clinical studies and shown to be immunogenic, efficacious, safe and well-tolerated with only mild side effects in adults, previously infected children (1-3 years old) and infants. Below is a short overview of the immunogenicity, efficacy, reactogenicity and safety results of the currently completed studies.

Immunogenicity and reactogenicity

In two placebo-controlled, double-blind clinical studies conducted in Finland, infants received two doses of the vaccine at approximately 2 and 4 months of age. GSK Biologicals' HRV vaccine was immunogenic in terms of anti-rotavirus IgA antibody seroconversion rate and geometric mean antibody concentrations (GMC). RV shedding was observed in 37.5-60% of the subjects at 7-9 days after the first dose.

Results from the first pilot efficacy study in Finland (Study 004) showed that two doses of the HRV vaccine were effective in preventing RV GE. The vaccine showed 71.6% (95% confidence interval (CI): 41.6-86.8) efficacy in preventing any RV GE and 84.9% (95% CI: 41.5-97.3) efficacy in preventing severe RV GE (an episode with a score $\geq$ 11 on the 20-point Vesikari scale [Ruuska, 1990]) during the entire follow-up period over two RV epidemic seasons after vaccination. Of note, G1 serotype was the most prevalent circulating serotype during both RV epidemic seasons.

Results from a phase IIb, double-blind, randomized, placebo-controlled study (Study 006) in Latin America (Brazil, Mexico and Venezuela) confirmed the efficacy of the HRV vaccine in preventing RV GE in infants in a setting with different circulating serotypes. This study assessed the reactogenicity, safety, immunogenicity and efficacy of two doses of the HRV vaccine at three virus concentrations ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu) in healthy infants when given at approximately 2 and 4 months of age concomitantly with routine vaccinations (i.e. diphtheria and tetanus toxoids, whole-cell pertussis and hepatitis B [DTPw-HB] and Hib). For the first year efficacy follow-up, the protective efficacy of the HRV vaccine (pooled HRV vaccine groups), in a setting where G1 and non-G1 serotypes circulate, was 61.4% (95% CI: 42.3-74.1) against any RV diarrhea, 74.1% (95% CI: 55.8-85.0) against severe RV diarrhea (an episode with a score $\geq$11 on the 20-point Vesikari scale [Ruuska, 1990] (refer to Table 12) and 79.0% (95% CI: 48.0-92.0) against hospitalized RV diarrhea. The best protective profile against severe RV disease was observed with the viral concentration of $10^{5.2}$ ffu or higher. This allowed for the dose selection for the phase III trial ($10^{5.8}$ ffu): the protective efficacy of the $10^{5.8}$ ffu HRV vaccine group (N=463) was 70.0% (95% CI: 45.7-84.4) against any RV diarrhea, 85.6% (95% CI: 63.0-95.6) against severe RV diarrhea and 79.0% (95% CI: 24.9-96.1) against

hospitalized RV diarrhea. The vaccine efficacy against severe RV GE for the pooled HRV vaccine groups was 78.1% (95% CI: -91.1-98.2) for the second year efficacy follow-up and 74.7% (95% CI: 37.7-90.1%) for the combined efficacy follow-up periods.

In the above mentioned studies the adverse events observed in infants vaccinated with the HRV vaccine were similar to those observed in the placebo group. Additional clinical trials have been also conducted in Singapore and South Africa. The HRV vaccine was co-administered with routine recommended vaccines and found to be well-tolerated and immunogenic.

Safety

As of 31 March 2004, over 74,450 infants have been enrolled in clinical trials with GSK Biologicals' HRV vaccine and a total of 2720 serious adverse events (SAEs) have been reported. Up to 31 March 2004, 28 SAEs have been reported as possibly related to HRV vaccination.

In view of the history of Rotashield® as discussed above, IS is a particular point of interest in the safety evaluation. A large phase III multi-country trial rota-023 is ongoing in Latin America and Finland. The main focus of this study is safety and occurrence of IS. Over 63,000 children are enrolled in this study and data remain blinded at this time. An Independent Data Monitoring Committee (IDMC) has been appointed to monitor the safety aspects in all trials and that includes a review of all SAE unblinded by treatment group, all case fatalities, and all IS cases during the HRV vaccine clinical development trials, including study rota 023.

As of 18 May 2004, IS has been identified in 39 children in the entire HRV development program**.** Four of these 39 cases have been unblinded. Two of these unblinded cases (one in the placebo group and one in the HRV vaccine group) occurred remotely from vaccination: one case at 6 months and the other one at 11 months after vaccination. The two other unblinded cases (both in the HRV vaccine group) occurred at respectively 6 and 15 days post-vaccination. Of the 35 cases that are still blinded, 33 cases were reported by HRV vaccine or placebo recipients in the ongoing rota-023 study. Of these 33 cases, 17 cases occurred remotely from vaccination (at least 41 days post vaccination), 2 cases occurred between Day 31 and Day 40 post vaccination and 14 cases were in the 0-30 Day risk window. For these 33 blinded cases it is not known to the study sponsor if the children received HRV vaccine or placebo. All IS cases were diagnosed promptly and treated immediately. Most children recovered completely and are in good health. The IDMC is reviewing all data on an ongoing basis and has expressed no safety concerns up to their last review through a statement issued in May 2004. The IDMC will continue to monitor all new data also during the course of this study rota 036.

Please refer to the latest version of the investigator brochure (Edition 5) for a detailed review of information on the HRV vaccine

1.2. Rationale for the study

This study will evaluate the efficacy, safety and immunogenicity of GSK Biologicals' HRV study vaccine at the selected optimum dose in healthy infants and will provide specific data in the European setting. The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis during the period starting 2 weeks after the second dose of study vaccination and ending at Visit 5 (mid-June to end-July 2005). Efficacy evaluation will continue during the second efficacy follow-up period that will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006).

This study will also assess the immune response to concomitantly administered childhood vaccinations. The co-administration of routine childhood vaccines with the HRV vaccine has been studied in other trials and no interference on immunogenicity was found. However, co-administration of some specific combination childhood vaccines in use in Europe has not been tested yet. This study will therefore evaluate concomitant administration of some specific childhood vaccines currently recommended in Europe. Subjects in each participating country will receive combination childhood vaccines that comply with the current local national Plan of Immunization schedule concomitantly with each HRV vaccine or placebo dose.

This study will further evaluate factors that are useful in understanding the epidemiology of RV infections in a European context, e.g. age of child at time of first RV infection, influence of breastfeeding, number of siblings and attendance to day care as risk factor. To that effect additional data such as demography and feeding practices will be collected for exploratory analyses.

2. OBJECTIVES

2.1. Primary objective

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Definitions

GE: Diarrhea with or without vomiting.

RV GE for efficacy analysis: An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.

Severe RV GE: An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system [Ruuska, 1990]). Additional alternative scoring systems may be evaluated (exploratory analyses, see Sections 8.12 and 10.6.2).

Efficacy follow-up period: All subjects will be followed over two efficacy follow-up periods. Study enrolment will start September 2004. The first efficacy follow-up period will begin 2 weeks after Dose 2 of study vaccination and end at Visit 5 (mid-June to end-July 2005). The second efficacy follow-up period will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006) covering approximately 12 months.

Also, refer to Glossary of Terms for definition of terms used.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

Efficacy

First efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- To assess vaccine efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season.

Second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Combined efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or

hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in the immunogenicity and reactogenicity subset, N=1800)

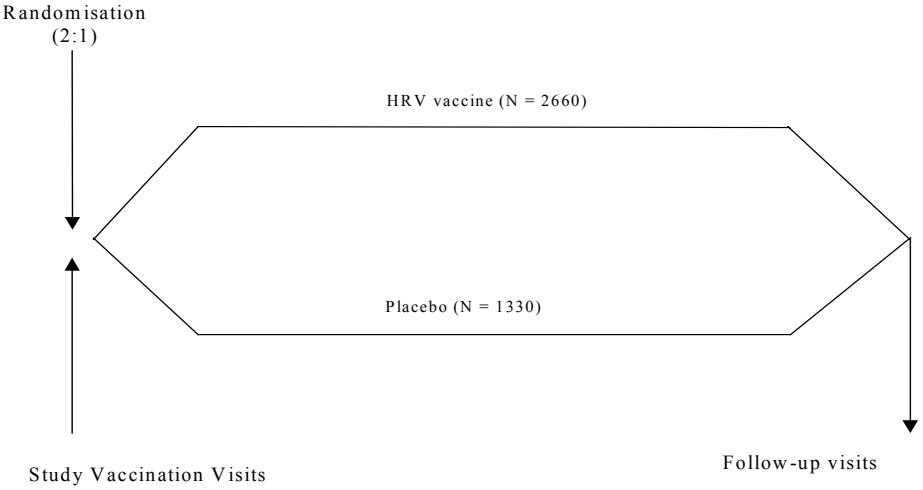
- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccines (depending on the vaccination schedule in respective participating countries, Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® or Meningitec® vaccines will be co-administered; in case of problems with availability of Meningetec® a similar alternative that is approved in Spain can be considered).

Safety and reactogenicity

- In the immunogenicity and reactogenicity subset (N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (31 days after each dose) and serious adverse events during the entire course of the study.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW



*At 7 months of age only for subjects from Spain ***(optional)***.
#At 12 months of age only for subjects from Italy ***(optional)***. At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" ***(optional)***. **(Amendment 1: 07 June 2005)**

- Experimental design: Double-blind, randomized, placebo-controlled, multi-country and multi-center study with two parallel groups.
- Control: Placebo (The placebo consist of all components of the study vaccine i.e. excipients and buffer, but no rotavirus particles).
- Blinding: Double-blind. See section 6.5 for details of blinding procedure.
- Treatment allocation: Randomized (2:1 ratio). See section 6.4 for a detailed description of the randomization method.
- Treatment Groups:

  Group HRV vaccine (N=2660): subjects will receive two doses of HRV vaccine co-administered with specific childhood vaccines

  Group Placebo (N=1330): subjects will receive two doses of placebo co-administered with specific childhood vaccines
- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months
  Finland: 3, 5, ***11***-12 months **(Amendment 1: 07 June 2005)**
  France and Germany: 2, 3, 4 months.
  Italy: 3, 5, 11 months
  Spain: 2, 4, 6 months

- Vaccination schedule: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.
- Concomitant vaccinations:

➢ In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing diphtheria and tetanus toxoids and acellular pertussis (DTPa), *Haemophilus influenzae* type b (Hib), Hepatitis B vaccine (HBV), and inactivated poliovirus vaccine (IPV)] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

- In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

  - Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
  - Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

  Thereafter, routine vaccinations will be given as per the recommended respective national Plan of Immunisation schedule of each country.

- Study visits: All subjects will have five study visits (Visits 1, 2, 3, 5 and 7). Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** have ***if necessary*** one additional visit (Visit 6). **(Amendment 1: 07 June 2005)**

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=1800), Dose 1 (HRV vaccine or placebo) and Dose 1 specific childhood vaccines.

  Visit 2 (Month 1 or 2) – Dose 2 (HRV vaccine or placebo), Dose 2 specific childhood vaccines, follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Visit 3 (Month 3 or 4) – Post-vaccination blood sample from a subset of subjects (N=1800), follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

  Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines. The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain, Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). Subjects in the Czech Republic, France and Germany will not require a separate visit since the blood sampling at post Dose 3 of the childhood vaccines coincides with Visit 3.

  Visit 4 ("immunogenicity and reactogenicity subset" in Spain only) one month after the third dose of the primary vaccination course at 7 months of age – Post-vaccination blood sample from all subjects in Spain (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 5 (mid-June to end-July 2005) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Visit 6 ("immunogenicity and reactogenicity subset" in Italy and Finland only) one month after the third dose of the primary vaccination course

In Italy: Visit 6 at 12 months of age – Post-vaccination blood sample from all subjects in Italy (N= 300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

In Finland: Visit 6 at 13 months of age – Post-vaccination blood sample from a subset of subjects (N= 300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 7 (mid-June to end-July 2006) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs) and study conclusion.

- Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject’s parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

  For each GE episode occurring during the study period, a GE diary card should be completed daily until end of the GE symptoms. During each GE episode, a stool sample(s) should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms.

- Specific solicited symptoms occurring during the 8-day follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo will be recorded by parents/guardians of a subset of subjects (N=1800) using diary cards. Unsolicited symptoms occurring within 31 days (Day 0-Day 30) after each study vaccine dose and SAEs during the entire study period will be recorded in all subjects. Parents/guardians will be asked to contact the investigator or his/her delegate in case of SAEs or IS during the study. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as

contact through telephone call, SMS using cellular phone, an Independent Calling Centre or other convenient means).

- An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case is reviewed by this committee.
- Duration of the study: Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per subject, will not exceed a total of maximum of 24 months.
- Data collection: Remote Data Entry (RDE).
- Refer to Appendix C for a summary of the recruitment plan.

4. STUDY COHORT

4.1. Number of subjects / centres

Total target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group). Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

All enrolled subjects will be followed for efficacy and safety.

Subjects will be enrolled at multiple sites in up to six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain). A target total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.

A subset of 1800 subjects (target 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

Enrolment will be terminated when 3990 subjects have been enrolled.

Refer to Appendix C for a summary of the recruitment plan.

4.2. Inclusion criteria

All subjects must satisfy the following criteria at study entry:

- Subjects who the investigator believes that their parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits, collection of stool samples) should be enrolled in the study.
- A male or female between, and including, 6 and 14 weeks (42 – 104 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Birth weight > 2000g.

4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If any apply, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)
- History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B disease (in all subjects). Only for subjects in Spain: history of meningococcal group C disease. Only for subjects in France and Germany: history of disease caused by *Streptococcus pneumoniae*.
- History of use of experimental rotavirus vaccine.
- Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (in all subjects). Only for subjects in Spain: previous vaccination against meningococcal group C. Only for subjects in France and Germany: previous vaccination against *Streptococcus pneumoniae*.
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract, IS or other medical condition determined to be serious by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

- Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).)
- Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).
- A family history of congenital or hereditary immunodeficiency.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- History of any neurologic disorders or seizures.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests

4.4. Elimination criteria during the study

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants 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 study vaccine(s) and ending 14 days after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

4.5. Contraindications to subsequent vaccination

GSK Biologicals' HRV vaccine or placebo:

The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 0):

- Hypersensitivity reaction due to the vaccine.
- IS.

The following AEs constitute contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs 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 5.4), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).

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

Co-administered vaccines:

For detailed information on Infanrix Hexa®, Infanrix Polio Hib®, *Neisseria meningitidis* C vaccine (e.g. Meningitec®) and *Streptococcus pneumoniae* vaccine (e.g. Prevenar®) to be co-administered with HRV vaccine or placebo, please consult the summary of product characteristics of the respective product in each country.

DTP vaccines (including Infanrix Hexa® and Infanrix Polio Hib®)

The following AEs constitute absolute contraindications to further administration of DTP vaccine; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine 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 AE:

Absolute contra-indications:

- Hypersensitivity reaction due to the vaccine.
- Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.

The following AEs constitute contraindications to administration of the study vaccine at that point in time; if any one of these AEs 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 AE.

- Acute disease at the time of vaccination. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).

- Axillary temperature ≥37.5°C (99.5°F) / Rectal temperature ≥38°C (100.4°F) / Oral temperature ≥37.5°C (99.5°F).

Precautions:

- Fever of ≥40.5°C (rectal temperature) or ≥40.0°C (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 occurring within 48 hours of vaccination and lasting ≥ 3 hours.
- Seizures with or without fever occurring within 3 days of vaccination.

Meningitec®

Absolute contraindications include:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- Acute severe febrile illness.

Prevenar®

Absolute contraindications include:

- Hypersensitivity to any component of the vaccine, including diphtheria toxoid.
- Acute severe febrile illness.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 version of 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. The ICH Harmonized Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. 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 provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator and/or sponsor.

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 the IRB/IEC by the investigator and/or sponsor. Written unconditional approval of the IRB/IEC must be in the possession of the investigator and GSK Biologicals before commencement of the study. 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. Relevant GSK Biologicals' data will be supplied by the investigator and/or sponsor to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of IRB/IEC unconditional approval of the protocol and the written informed consent statement will be transmitted by the investigator to the Site Monitor using the standard notification form, prior to shipment of vaccine supplies and the electronic case report forms (eCRFs)/RDE system to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval of an appropriate amendment. Administrative changes are submitted to the IRB/IEC for information only. However, written verification that the administrative change was submitted should be obtained. Approvals/ verifications must be transmitted in writing to the Site Monitor by the investigator.

The IRB/IEC must be informed by the investigator and/or sponsor of:

- all subsequent protocol amendments, 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 administrative changes (for information, except for US studies),
- 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.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator and/or sponsor must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical

principles that have their origin in the October 1996 version of the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to the subjects' parents/guardians.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects' parents/guardians face to face. The Informed Consent Form may be read to the subjects' parents/guardians, but, in any event, the investigator or designate shall give the subjects' parents/guardians ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects' 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 parents/guardians and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the parents'/guardians' incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The parents/guardians should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects' parents/guardians, and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects' parents/guardians.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects' parents/guardians should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's parents'/guardians' responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects' parents/guardians should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects' parents/guardians for participating in the trial.

l. The anticipated expenses, if any, to subjects' parents/guardians for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects' parents/guardians may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the 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 subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject's parents/guardians is authorizing such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects' parents/guardians will be informed in a timely manner if information becomes available that may be relevant to the subjects' parents/guardians willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent

form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

5.2. General study aspects

- There will be no restrictions on feeding the infants before or after study vaccine administration.
- All vaccines administered in the period beginning at birth and ending at the blood sampling visit after completion of the routine three-dose primary vaccination course should be documented in the eCRF.
- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months
  Finland: 3, 5, ***11***-12 months **(Amendment 1: 07 June 2005)**
  France and Germany: 2, 3, 4 months.
  Italy: 3, 5, 11 months
  Spain: 2, 4, 6 months

- In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing DTPa, HBV, Hib and IPV] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

- In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

  - Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
  - Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

  Thereafter, routine vaccinations will be given as per the recommended local national Plan of Immunisation schedule.

- All subjects in all countries will have five study visits (Visits 1, 2, 3, 5 and 7). In addition, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" (target N=300 per country) ***may*** have ***if necessary*** an additional study visit because the blood sampling timepoint one month post Dose 3

of the childhood vaccines in these countries does not ***always*** coincide with study visits planned for all subjects. Blood samples will be taken at the additional visit to evaluate immunogenicity of routine vaccines The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain, Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). **(Amendment 1: 07 June 2005)**

- The study will further evaluate factors that are useful in understanding the epidemiology of RV infections in a European context, e.g. age of child at time of first RV infection, influence of breastfeeding, number of siblings and attendance to day care as risk factor. To that effect additional data will be collected, at the time of the scheduled visits or using the GE diary cards.

5.2.1. Independent Data Monitoring Committee (IDMC)

An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case and each case fatality is reviewed unblinded by treatment group by this committee.

5.2.2. Surveillance of SAEs and IS

Parents/guardians of all subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as contact through the Independent Calling Centre or another convenient means).

The investigators will be asked to inform the parents/guardians of the signs and symptoms of IS. Symptoms consistent with IS are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. Parents/guardians/caretakers of study subjects will be instructed to seek medical advice at the nearest hospital in case of symptoms indicative of IS, and to inform the investigator. The investigator and his staff will take appropriate actions to treat the condition. Refer to Appendix H for information on follow-up of IS cases and refer to Appendix D for information on handling of biological samples collected during IS cases.

5.2.3. Follow-up of GE episodes and collection of stool samples

Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to

end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

For each suspected GE episode occurring during the study period, a GE diary card should be completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE episode will be recorded on the same card. The completed diary cards should be returned to the investigator at the following study visit. The investigator will verify the returned completed GE diary card and (s)he or study personnel will transcribe the information into the appropriate sections of the eCRF, in English.

For each suspected GE episode occurring during the study period, a stool sample should be obtained from the subject. The stool sample should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms. The stool sample should be stored at refrigerator temperature (approximately 2-8°C) until it is transferred rapidly to the investigator's laboratory (within 0-3 days). The stool sample should be stored frozen at approximately - 20°C or colder until shipped to GSK Biologicals (Please refer to Appendix D and Appendix E).

5.3. Subject identification

Subject numbers will be assigned sequentially to subjects contacted by study investigators, according to the range of subject numbers allocated to each study centre. Refer to Section 6.4 for a detailed description of treatment allocation and randomization.

5.4. Outline of study procedures

Table 1 List of study procedures at visits planned for all subjects in all countries

(Amendment 1: 07 June 2005)

Age **Visit §** **Timing** **Sampling timepoint**	**6-14 weeks** **VISIT 1** **Day 0** **Pre**	**VISIT 2** **Month 1 or 2**	**VISIT 3** **Month 3 or 4** **Post vacc 2**	**VISIT 5**	**VISIT 7**
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●‡		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in a subset: for antibody determination	● (1 ml) (N=1800)		● (3 ml) (N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations∗	●	●			
Recording all childhood vaccinations	●	●	●	● ***Finland/Italy only***	
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)	●	●			
Return of reactogenicity diary cards in a subset (N=1800)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination#	●	●	●	●	
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●
Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

§Additional visits ***can be*** planned ***if necessary*** for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset": Visit 4 will take place in Spain only and Visit 6 take place in Finland and Italy only. Visit 4 and Visit 6 are not applicable for France, Germany and the Czech Republic. Refer to Table 2 for more details. **(Amendment 1: 07 June 2005)**

Note: The double-line border following Month 3 indicates the interim analysis which will be performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

∗ The third dose of the routine childhood vaccine(s) must be given according to the respective national Immunisation plans of each country. A study visit is not planned specifically for administration of third dose of the routine childhood vaccine(s).

#According to guidelines specified in Section 6.9

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

(Amendment 1: 07 June 2005)

Age **Visit** **Timing** **Sampling timepoint**	**VISIT 4** **SPAIN only** **Month 5** **Post-vacc 2∗**	**VISIT 6** **ITALY only** **Month 9** **Post-vacc 2∗**	**VISIT 6** **FINLAND only** **Month 10** **Post-vacc 2∗**
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●‡	●‡	●‡
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in a subset: for antibody determination (3 ml)	● (target N=300 from Spain)	● (target N=300 from Italy)	● (target N=300 from Finland)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)			
Return of reactogenicity diary cards in a subset (N=1800)			
Transcription of the reactogenicity diary card in a subset (N=1800)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination#	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of routine childhood vaccinations.

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

#According to guidelines specified in Section 6.9

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject's evaluability in the according to protocol analyses (see Sections 4.4 and 10.4 for details of criteria for evaluability and cohorts to be analyzed).

The local national Plan of Immunization schedules vary from country to country. The local immunization schedule should be followed to administer study vaccine concomitantly with specific childhood vaccinations at Visit 1 and Visit 2. In order to assess the safety of the study vaccine, the interval between two study vaccine doses should not be less than 30 days. Table 3 presents the interval between study visits to be followed in each specified country. Table 4 presents the age at each visit per country.

Table 3 Intervals between study visits

(Amendment 1: 07 June 2005)

Interval	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Routine schedule	**3, 4, 5 months**	**3, 5, *11*-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccines
End of the 1st efficacy follow-up period	mid-June to end-July 2005				
one month after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable
End of the 2nd efficacy follow-up period	mid-June to end-July 2006				

Table 4 Age of the subjects at each study visits

Age at Visit	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Visit 1	3 months	3 months	2 months	3 months	2 months
Visit 2	4 months	5 months	3 months	5 months	4 months
Visit 3	6 months	6 months	5 months	6 months	6 months
Visit 4	Not applicable				7 months
Visit 5	Will vary (Visit to be completed by mid-June to end-July 2005)				
Visit 6	Not applicable	13 months	Not applicable	12 months	Not applicable
Visit 7	Will vary (Visit to be completed by mid-June to end-July 2006)				

5.5. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

Visit 1: Dose 1 of study vaccine (6-14 weeks of age)

- Written informed consent from the parent/guardian of the subject.
- Medical history taking.
- Physical examination and recording of height and weight.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Check of inclusion/exclusion criteria.
- Check contraindications to vaccination.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF.
- Record feeding practice.
- Randomization (or subject) number attribution.
- Collection of pre-vaccination blood sample for serology from a subset of subjects (N=1800): a minimum of 1 ml of whole blood to provide a minimum of 0.6 ml of serum according to instructions in Appendix D.
- Study vaccination: Oral administration of Dose 1 of the HRV vaccine or its placebo according to the guidelines set out in Section 6.2.
- Administration of specific vaccines to be co-administered with HRV vaccine or placebo dose. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be 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.
- Diary cards will be provided to the parents/guardians of all subjects to record unsolicited AEs (except GE) and medication between Visit 1 and Visit 2. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.

- Reactogenicity diary cards will be provided to the parents/guardians of a subset of subjects (N=1800) to record specific solicited general adverse experiences occurring during the 8-day (Day 0 to Day 7) solicited follow-up period after Dose 1 of the study vaccine or placebo. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- All parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Day 8 after Dose 1 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Interval between Visit 1 and Visit 2

Day 0 to Day 7 after Dose 1:

- The parents/guardians of a subset of subjects (N=1800) should record information on specific solicited general adverse experiences in the provided reactogenicity diary card.

Between Visit 1 and Visit 2

- Starting from Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians of all subjects should record information on any unsolicited AEs (except GE) and medications in the provided diary card.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 2: Dose 2 of study vaccine (30-48 days after Visit 1 in the Czech Republic, France and Germany / 49-83 days after Visit 1 in Finland, Italy and Spain)

- Physical examination.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Check of the appropriate elimination criteria.

- Collection and verification of the completed unsolicited AE/medication diary card from all subjects.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Recording of any unsolicited AEs within 31 days (Day 0 to Day 30) after Dose 1 of the study vaccine and any SAEs/IS that may have occurred since Visit 1 in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Check contraindications to vaccination.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Collection of the completed reactogenicity diary cards from a subset of subjects (N=1800). The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Record feeding practice.
- Study vaccination: Oral administration of Dose 2 of the HRV vaccine or its placebo according to the guidelines set out in Section 6.2.
- Administration of specific vaccines to be co-administered with HRV vaccine or placebo dose. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be 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.
- Diary cards will be provided to the parents/guardians of all subjects to record unsolicited AEs (except GE) and medication between Visit 2 and Visit 3. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Reactogenicity diary cards will be provided to the parents/guardians of a subset of subjects (N=1800) to record specific solicited general adverse experiences occurring during the 8-day (Day 0 to Day 7) solicited follow-up period after Dose 2 of the study vaccine or placebo.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Day 8 after Dose 2 until the next visit. The parents/guardians will be instructed to return their completed diary cards to

the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Interval between Visit 2 and Visit 3

Day 0 to Day 7 after Dose 2:

- The parents/guardians of a subset of subjects (N=1800) should record information on specific solicited general adverse experiences in the provided reactogenicity diary card.

Between Visit 2 and Visit 3

- Until end of May 2005, each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians of all subjects should record information on any unsolicited AEs (except GE) and medications in the provided diary card.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries, including between visits if applicable. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.

Visit 3: Follow-up (30-48 days after Visit 2 in Finland and Italy / 49-83 days after Visit 2 in the Czech Republic, France, Germany and Spain)

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- Check of the appropriate elimination criteria.
- Collection and verification of the completed unsolicited AE/medication diary card from all subjects.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.

- Recording of any unsolicited symptoms within 31 days (Day 0 to Day 30) after Dose 2 of the study vaccine and any SAEs/IS that may have occurred since Visit 2 in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Collection of post-vaccination blood sample for serology from a subset of subjects (N=1800): a minimum of 3 ml of whole blood to provide a minimum of 1.2 ml of serum according to instructions in Appendix D.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Collection of the completed reactogenicity diary cards from a subset of subjects (N=1800). The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 3 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.
- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries, including at or between visits if applicable. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.

Between Visit 3 and Visit 5

- From December 2004 to end of May 2005, each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries, including between visits if applicable. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.

Visit 4 (at 7 months of age): Only for subjects in Spain.
Visit 4 is optional and may be combined with Visit 5.
(Amendment 1: 07 June 2005)

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- Check of the appropriate elimination criteria.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Collection of post-vaccination blood sample for serology from all subjects in Spain: a minimum of 3 ml of whole blood to provide a minimum of 1.2 ml of serum according to instructions in Appendix D.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 4 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Visit 5 (mid-June to end-July 2005): End of the first efficacy follow-up period

- Check of the appropriate elimination criteria.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate

sections of the electronic case report form, in English. The study monitor may help in this translation.

- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 5 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.
- Administration of the routine childhood vaccinations should be given in accordance with the national Immunisation plans in the respective countries. All vaccines should be administered according to the guidelines set out in Section 6.2. All co-administered vaccines should be recorded in eCRF.
- Conclusion of Visit 5.

Between Visit 5 and Visit 7

- Between Visit 5 and December 2005, each subject's parent/guardian will be contacted biweekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE.
- Between December 2005 to end of May 2006 each subject's parent/guardian will be contacted weekly by telephone, SMS, an Independent Calling Centre or another convenient means to check on the occurrence of any GE. Bi-weekly contact will take place from June 2006 until study end.
- During each GE episode, the GE diary card should be completed by the parents/guardians daily until end of the GE symptoms.
- During each GE episode, parents/guardians of all subjects should collect a stool sample from the subject and return it to the investigator on an ongoing basis.
- Parents/guardians should contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 6: Only for subjects from the "immunogenicity and reactogenicity subset" in Italy at 12 months of age and in Finland at 13 months of age.
Visit 6 is optional and may be combined with Visit 5
(Amendment 1: 07 June 2005)

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and***

appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

- Check of the appropriate elimination criteria.
- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Collection of post-vaccination blood sample for serology in a subset of subjects: a minimum of 3 ml of whole blood to provide a minimum of 1.2 ml of serum according to instructions in Appendix D.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- A GE diary card will be provided to parents/guardians of all subjects to record information on any GE episodes occurring from Visit 6 until the next visit. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D.

Visit 7 (mid-June to end-July 2006): End of the second efficacy follow-up period

- Check of the appropriate elimination criteria.
- Collection of any stool samples (in case of GE).
- Collection of the completed GE diary cards from all subjects. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the electronic case report form, in English. The study monitor may help in this translation.
- Recording of any SAEs/IS that may have occurred since the previous visit in the eCRF.
- Record any AEs leading to drop out that may have occurred since the previous visit in the eCRF.
- Recording of any prior/concomitant medication or vaccination administered in the eCRF, according to the guidelines set out in Section 6.9.
- Conclusion of Visit 7 and study end.

5.6. Sample handling and analysis

5.6.1. 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.

5.6.2. Laboratory assays

5.6.2.1. GE stool analysis

Stool samples collected during GE episodes will be processed at the study site and shipped frozen to GSK Biologicals, Belgium for further distribution to the core laboratories where analysis will be performed.

All GE stool samples will be analysed by ELISA for detection of RV. If a stool sample tests positive for RV, the sample will be tested by Polymerase Chain Reaction (PCR) to determine the serotype. If any G1 rotavirus is detected in the stool specimens between Visit 1 to Visit 3, vaccine virus will be differentiated from the wild type serotype by sequence analysis or an equivalent approach.

Any additional testing on stool samples will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine

5.6.2.2. Serum analysis

Refer to Section 6.4.3 for information on the subset of subjects who will provide blood samples. Blood samples collected from a subset of subjects at each sampling time point will be centrifuged and the separated serum should be stored at –20°C until shipped to the sponsor for analysis.

All serological assays will be performed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.

Anti-rotavirus IgA antibody concentrations will be measured in all serum samples collected at Visit 1 and Visit 3.

Other assays will be performed depending on the specific vaccines co-administered with each HRV vaccine or placebo dose. Antibodies to all antigens contained in the co-administered vaccines will be measured at each sampling time point [i.e. Visit 3 (all countries), Visit 4 (Spain) and Visit 6 (Italy and Finland)]. In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity ***and ELISA test***, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP. **(Amendment 1: 07 June 2005)**

Table 5 summarizes the laboratory assays to be performed on the serum samples.

Table 5 Laboratory Assays

(Amendment 1: 07 June 2005)

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
rotavirus	IgA ELISA	in-house	U/ml	20
anti-D	ELISA	in-house	IU/ml	0.1
anti-T	ELISA	in-house	IU/ml	0.1
anti-PT	ELISA	in-house	EL.U/ml	5
anti-FHA	ELISA	in-house	EL.U/ml	5
anti-PRN	ELISA	in-house	EL.U/ml	5
anti-HBs	ELISA	in-house	mcg/ml	10
anti-poliovirus type 1	micro-neutralization test	in-house	ED50	8
anti-poliovirus type 2	micro-neutralization test	in-house	ED50	8
anti-poliovirus type 3	micro-neutralization test	in-house	ED50	8
anti-PRP	ELISA	in-house	mcg/ml	0.15
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	***In-house***	***mcg/ml***	***0.3***
Antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide*	ELISA	in-house	mcg/ml	0.05

U = units
IU = International units
EL.U = Elisa units
ED 50 = Estimated dose 50%
#For samples from Spain only
*For samples from France and Germany only

Any additional testing on serum samples will be performed if deemed necessary by GSK Biologicals if any findings concerning toxicity or immunogenicity in the present study or in other studies necessitate further investigations.

Refer to Appendix F for details on laboratory assays.

5.6.3. IS samples

Refer to Appendix H for information on analysis of biological samples collected for IS.

The GSK Biologicals' designated laboratories will test:

- Frozen stool samples or rectal swab and throat swab specimens by RT-PCR to determine the presence of RV, enteroviruses and adenoviruses.

- Acute and convalescent blood samples will be tested to detect an acute antibody response to RV. Blood and/or stool and/or throat swab tests will be tested for the presence of a range of suspected pathogens. Also, histopathologic evaluation of tissue will be conducted.
- In case of surgical resection, a surgical specimen of any enlarged mesenteric lymph node should be obtained. If bowel or the appendix is resected, these specimens also should be included in the evaluation. As molecular assays are to be performed on these surgical specimens, the use of powderless gloves, RNAse-free pipettes, aerosol RNAse-free tips, non-autoclaved disposable plasticware/forceps, commercial PBS solution/water/Formaldehyde solutions as well as limited steps of the solution preparation are highly recommended to avoid RNAse contamination. Refer to the lab workbook for the process of resected tissue. Testing including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR will be arranged by GSK Biologicals in consultation with the Attending Pathologist.
- Fresh stool samples may be tested locally according to standard microbiologic methods for the presence of any suspected enteric pathogens, e.g. Salmonella, Shigella, Campylobacter, Yersinia, and others.

Any additional testing on biological samples collected for IS will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine.

5.6.4. Serology and stool analysis plan

Table 6 presents the plan for analyses of serum and stool samples collected during the study.

Table 6 Serology and Stool Analysis Plan

(Amendment 1: 07 June 2005)

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times during the study			RV	all	none
Serology					
Pre	0	1	HRV	Immunogenicity subset (N=1800)	none
Post-vacc 2∗	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP, 7 *S. pneumoniae* serotypes (France and Germany only)	Immunogenicity subset ***except Spain*** (N=1~~5~~800)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	***3***	***HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)***	***N=300 from Spain***	***HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.***
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity ***and ELISA test***	N=300 from Spain	***Men C*** serum bactericidal activity ***and ELISA test***, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	9	6 (Italy only)	, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP	N=300 from Italy	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP
	10	6 (Finland only)	, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP	N=300 from Finland	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP

∗Post Dose 2 of study vaccine for all countries. Depending on the local national Plan of Immunisation schedule in each country, may be post Dose 2 or post Dose 3 of routine childhood vaccines

#Corresponds to Post Dose 3 of routine childhood vaccines in the respective countries.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to the priority ranking specified in Table 6.

5.6.5. Endpoints for suboptimal response

Not applicable.

6. INVESTIGATIONAL PRODUCTS AND ADMINISTRATION

6.1. Study vaccines

The candidate vaccine, placebo and diluent to be used have been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for each product are described in separate release protocols and the required approvals have been obtained.

Table 7 presents the composition of the study vaccine.

Table 7 Study vaccine composition

Vaccine	Formulation	Presentation	Volume
GSK Biologicals' HRV vaccine	RIX4414 HRV strain $10^{6.5}$ CCID50 Dulbecco's Modified Eagle Medium (DMEM) 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilized vaccine in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' Placebo for HRV vaccine	DMEM 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilized vaccine in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' calcium carbonate buffer	Calcium carbonate 80 mg Xanthane 0.25 % in Water for Injection 1.3 ml	Liquid buffer in pre-filled syringe.	1.3 ml

One lot each of the HRV vaccine and placebo will be used.

GSK Biologicals' Infanrix Hexa®, Infanrix Polio Hib® ***and Prevenar*®** vaccines will be also supplied. These commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics. **(Amendment 1: 07 June 2005)**

Refer to Appendix G for details of vaccine supplies.

6.2. Dosage and administration

HRV vaccine or placebo

To prepare the HRV vaccine or placebo for administration, the entire content of the supplied calcium carbonate 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.

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Should the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered at that visit. The subject may continue to participate to the study and will not be excluded from the planned analyses.

Childhood vaccines to be co-administered with each study vaccine dose

Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® and Meningitec® vaccines should be prepared and administered according to the manufacturer's recommendations.

The vaccination regimen is summarized in Table 8.

Table 8 Dosage and Administration

Country	Visit	Vaccination	Dose	Vaccine[a]	Route[b]	Site[c]
Study vaccination						
All	1, 2	Rotavirus or its Placebo	1	HRV or placebo	O	not applicable
Childhood vaccines to be co-administered with each study vaccine dose						
All, except France	1, 2	DTPa, HBV, IPV, Hib	1	Infanrix Hexa®	IM	T
France	1	DTPa, HBV, IPV, Hib	1	Infanrix Hexa®	IM	T
	2	DTPa, IPV, Hib	1	Infanrix Polio Hib®	IM	T
France and Germany	1, 2	*Streptococcus pneumoniae*	1	Prevenar®	IM	D/ T
Spain	1, 2	*Neisseria meningitidis* C	1	Meningitec®	IM	D/ T

a. Vaccine/Control
b. Oral (O)/ Intramuscular (IM)
c. Deltoid (D)/ Thigh (T)

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Thereafter, routine vaccinations will be given as per the recommended local national Plan of Immunisation schedule. Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

6.3. Storage

(Amendment 1: 07 June 2005)

All vaccines must be stored in a safe and locked place with no access for unauthorized personnel.

Vaccines will be stored at the defined range of temperature (i.e. +2 to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of temperature deviation (temperature outside the defined range, i.e. +2 to +8°C/ 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

proper functioning was demonstrated during the monitor's site evaluation,

if the system continues to work in case of a power failure, and

if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working when after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag®) close to the vaccines as a back up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C/ 36°F to 46°F), must be reported within 24 hours to the Sponsor (i.e. Study Monitor/ GSK Local Contact/ GSK Biologicals)

Following exposure to a temperature deviation, vaccines will not be used until written approval is given by the sponsor.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.

6.4. Treatment allocation and randomization

Target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group).

6.4.1. Randomization of supplies

A randomization list will be generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and will be used to number the vaccines. A randomization blocking scheme (2:1 ratio) will be used to ensure that balance between treatments is maintained: a single treatment number will identify uniquely the vaccine doses to be administered to the same subject.

To allow GSK Biologicals 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, an over-randomization of supplies (not exceeding 20%) will be prepared.

The vaccine doses will be distributed to each study centre while respecting the randomization block size.

6.4.2. Randomization of subjects

The treatment allocation at the investigator site will be performed using a central randomization call-in system on Internet (SBIR). The randomization algorithm will use a minimization procedure stratified by vaccination sites.

After confirmation that the subject is eligible, the person who is in charge of the vaccination will access the randomization system on Internet. Upon providing a subject number for the subject, the randomization system will use the minimization algorithm to determine the treatment number to be used for the subject. Would Internet be unavailable the subjects would be administered the treatment number with the highest number still available at the vaccination site.

6.4.3. Subsets

A subset of 1800 subjects (target of 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

For Finland, 300 subjects enrolled at specific centre(s) will be part of the "immunogenicity and reactogenicity subset". For each of the other participating countries, all of the 300 enrolled subjects will be part of the "immunogenicity and reactogenicity subset".

6.5. Method of blinding and breaking the study blind

The study will be conducted in a double-blinded manner. The parents/guardians of the subjects, the study personnel including the study monitor and the investigator will be unaware of the administered treatment. Blinding will be maintained for the whole study period (see Section 10.7 for details on how the individual blinding will be maintained despite statistical analyses before all study data are collected/processed). This will allow unbiased evaluation of the study vaccine.

No set of individual codes will be held at the local GSK Biologicals' Safety Office or GSK Biologicals' Central Safety Office. The local GSK Biologicals' Safety Office will be able to access the individual randomization code from the central randomization system on the Internet. The GSK Biologicals' Central Safety Office will access the

individual randomization code using Matex (new randomization system). The code will be broken by the Clinical Safety physician (Study Contact for Emergency Code Break in Sponsor Information page) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s).

In the event that the code is broken, the reason must be recorded in the eCRF/RDE and in the subject's medical record.

The IDMC will be informed of each SAE including any IS cases on an ongoing basis. The IDMC will have access to the individual codes and may at its discretion decode the SAEs to identify the product administered to any subject and evaluate whether enrollment in the study should be halted.

6.6. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix G for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization when applicable), at least 5% additional doses will be supplied. In case a vaccine dose is broken or unusable, the investigator should replace it with a replacement vaccine dose. Although the sponsor need not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of the replacement vaccine must be recorded by the investigator on the vaccine administration page of the eCRF and on the vaccine accountability form.

The investigator will use the central randomization system (SBIR) to obtain the replacement vial number. The system will ensure, in a blinded manner, that the replacement vial is of the same formulation as the randomized vaccine.

6.7. Packaging

See Appendix G.

6.8. Vaccine accountability

See Appendix G.

6.9. Concomitant medication/treatment

At each study visit/contact, the investigator should question the subject's parents/guardian about any medication(s) taken.

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study

vaccine (HRV vaccine or placebo) are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever is later) are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment. Refer to Sections 4.3 and 4.4.

All vaccines administered in the period beginning at birth and ending at the blood sampling visit after completion of the routine three-dose primary vaccination course are to be recorded with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as ‘Prophylactic’.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for adverse events must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment. Refer to Section 8.2 for definition of SAE.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

Each subject’s parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.

Examples of an AE DO NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

N.B. AEs to be recorded as endpoints (solicited events) are described in Section 8.5.1. All other AEs will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study procedure) should be recorded in the medical history section of the subject's eCRF.

8.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which 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.

c. requires hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.2.1. Disease-related events or outcomes not qualifying as serious adverse events

Not applicable.

8.3. Lack of efficacy

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the AE or SAE definition (including clarifications).

8.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, ultrasound etc.) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1 or SAE, as defined in Section 8.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.5. Time period, frequency, and method of detecting adverse events and serious adverse events

All AEs occurring within 31 days following administration of each dose of vaccine/ placebo 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.

All AEs leading to subject withdrawal or drop out 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.

The standard time period for collecting and recording SAEs will begin at randomization or the first receipt of vaccine/ placebo and will end at the last study visit foreseen for each subject. See Section 8.8 for instructions for reporting and recording SAEs.

Additionally, in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. procedures, invasive tests, a change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

The investigator will inquire about the occurrence of AEs/SAEs at every visit/contact during the study.

All AEs either observed by the investigator or one of his clinical collaborators or reported by the subject's parent/guardian spontaneously or in response to a direct question will be evaluated by the investigator. AEs 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. Refer to Section 6.9.

As a consistent method of soliciting AEs, the subject's parent/guardian 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 AEs having occurred within the time frame defined above.

AEs already documented in the eCRF, i.e. at a previous assessment, and designated as "not recovered/not resolved" or "recovering/resolving" should be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the eCRF should be completed.

N.B. If an AE changes in frequency or intensity during the specified reporting period, a new record of the event will be entered.

When an AE leading to drop out/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE leading to drop out /SAE on the eCRF or SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed AE/SAE pages. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE leading to drop out /SAE and not the individual signs/symptoms.

8.5.1. Solicited adverse events

Solicited general AEs

Information on solicited symptoms will be collected for 8 days (Day 0 to Day 7) after each HRV vaccine or placebo dose by the parents/guardians of a subset of subjects (N=1800) using diary cards provided by the sponsor. Table 9 specifies the general AEs solicited during this study.

Table 9 Solicited general adverse events

Fever (Rectal/Axillary)
Fussiness/Irritability
Loss of appetite
Vomiting
Diarrhea
Cough/runny nose

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

8.6. Evaluating adverse events and serious adverse events

8.6.1. Assessment of intensity

Intensity of the following AEs will be assessed as described in Table 10.

Table 10 Intensity scales to be used by parents/guardians for solicited symptoms

Adverse Experience	Intensity grade	Parameter
Fever*		Record temperature in °C using a rectal/axillary 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
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 temperature ≥38°C (≥37.5°C) as measured by a rectal (axillary) thermometer.
¶Diarrhea is defined as passage of 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.

The maximum intensity of diarrhea, fever and vomiting occurring during the solicited 8-day follow-up period will be scored at GSK Biologicals as shown in Table 11.

Table 11 Intensity scales used at GSK Biologicals for diarrhea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	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
Fever	0	Rectal temperature < 38.0°C or axillary temperature < 37.5°C
	1	Rectal temperature ≥ 38.0 – ≤ 38.5°C or axillary temperature ≥ 37.5 – ≤ 38.0°C
	2	Rectal temperature > 38.5 – ≤ 39.5°C or axillary temperature > 38.0 – ≤ 39.0°C
	3	Rectal temperature > 39.5°C or axillary temperature > 39.0°C

The investigator will make an assessment of intensity for all other AEs, i.e. unsolicited symptoms reported within 31 days (Day 0-Day 31) after each study vaccine dose and AEs leading to drop out or SAEs reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE (unsolicited symptoms

or AE leading to drop out) and SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. (In a young child, such an AE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.2.

8.6.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE Report Form to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE Report Form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

Causality of all AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	The AE 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 AE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify).

8.6.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parents/guardians will be asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the eCRF.

8.7. Follow-up of adverse events and serious adverse events and assessment of outcome

After the initial AE (unsolicited symptom or AE leading to drop out)/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All AEs (unsolicited symptom or AE leading to drop out) and SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts.

Investigators will follow-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

- or, in the case of other non-serious AEs, until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any subject must be made available to the Study Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE Report Form, with all changes signed and dated by the investigator. The updated SAE report form should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.8.1.

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e. unsolicited AE), AE leading to drop out or any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.8. Prompt reporting of serious adverse events to GSK Biologicals

8.8.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. The investigator or designate will fax the SAE reports to GSK Biologicals' Study Contact for Serious Adverse Event Reporting **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS**. Additional or follow-up information relating to the initial SAE report is also to be reported to the GSK Biologicals' Study Contact for Serious Adverse Event Reporting within 24 hours of receipt of such information.

8.8.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours as outlined in Section 8.8.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received and forwarded to GSK **WITHIN 24 HOURS** as outlined in Section 8.8.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.6.2.

Facsimile (Fax) transmission of the SAE Report Form is the preferred method to transmit this information to the Study Contact for Reporting SAEs. The Study Contacts per country (where available) are provided as a separate protocol attachment (refer Attachment 1); in the case where the Study Contact is not available, you must contact the back-up Study Contact (see below). In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours as outlined in Section 8.8.1.

In the event of a death determined by the investigator to be related to vaccination, sending of the fax must be accompanied by telephone call to the Study Contact for Reporting SAEs.

(Amendment 1: 07 June 2005)

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [redacted] ***or*** [redacted] **24/24 hour and 7/7 day availability**

8.9. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.8. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

Expedited Investigator Safety Reports (EISR) are prepared according to GSK Biologicals policy and are forwarded to investigators as necessary. An EISR is required for:

- development compounds (i.e. compounds not marketed), if the event is serious, unexpected and has a suspected relationship to study drug treatment. Expected adverse events for development compounds will be described in the Development Core Safety Information (DCSI) in the Investigator Brochure (IB).
- marketed compounds (i.e. approved in at least one market), if the event is serious, unexpected and has a suspected relationship to treatment with a GSK product AND is a significant new emerging safety issue. Expected adverse events for marketed compounds will be described in the Core Safety Information (CSI). An EISR is required if an SAE was expedited to the IND in the US or to fulfil regulatory obligations in other countries. An EISR for Post marketing surveillance (PMS)/phase IV studies would not typically be required.

The purpose of the EISR is to fulfil specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an EISR describing a SAE or other specific safety information from GSK Biologicals will file it with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.10. Post study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 8.5. Investigators are not obligated to actively seek AEs or SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.11. Pregnancy

Not applicable.

8.12. Assessment of GE episodes

Any GE episode (defined as diarrhea with or without vomiting) starting from Visit 1 to study end should be documented using the GE diary card. The following information will be collected on the GE diary card during each GE episode: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be also recorded. The information collected

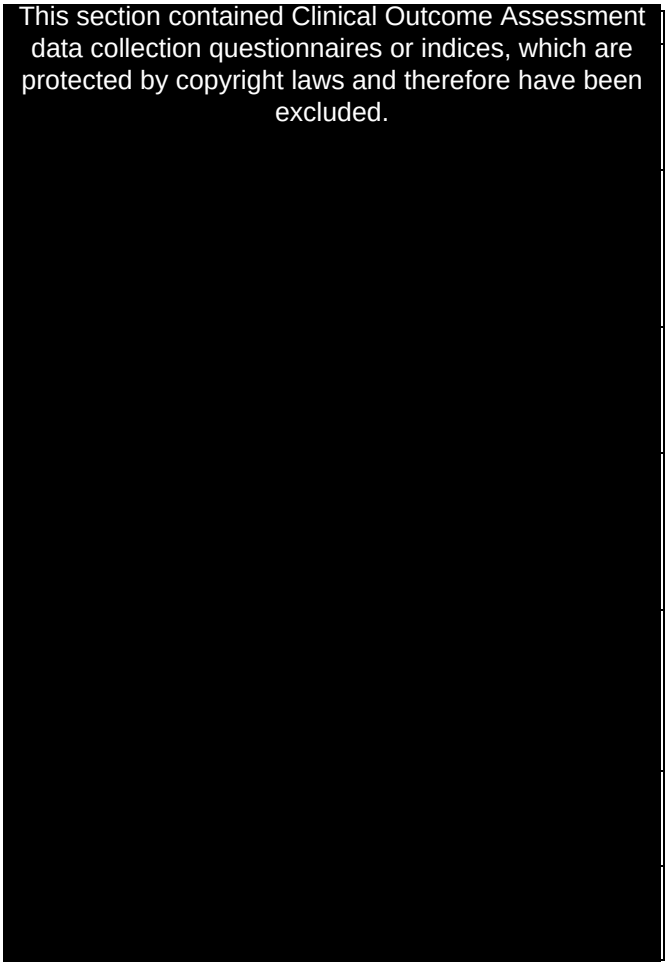
on the GE diary card will allow the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

Medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) will also be recorded for each GE episode.

Behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

In the 20-point scoring system [Ruuska, 1990], points will be assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalization (hospitalized subjects will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 12.

Table 12 The 20-point scoring system to determine the intensity of GE episodes reported during the study



∗ The highest temperature recorded during the episode will be scored.

A score < 7 is prospectively defined as mild, a score 7 - 10 is prospectively defined as moderate and a score ≥ 11 is prospectively defined as severe [Joensuu , 1997].

Periodic contact will be made with the subjects' family to enquire about the occurrence of GE, medical care or advice, and hospitalization. Collection of a stool sample will be requested if not yet provided and if GE occurred since last contact.

8.13. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.9.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Subjects who are withdrawn for AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (see Section 0).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study is any subject who did not come back for the concluding visit foreseen in the protocol.

A subject qualifies as a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented on the Study Conclusion page of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject's parent or guardian or the investigator and which of the following possible reasons was responsible for withdrawal:

- serious adverse event
- non-serious adverse event

- protocol violation (specify)
- consent withdrawal, not due to an adverse event
- moved from the study area
- lost to follow-up
- other (specify).

9.2.2. Subject withdrawal from investigational product

A 'withdrawal' from the investigational product is any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational product may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational product will be documented on the Vaccine Administration page of the eCRF. The investigator will document whether the decision to discontinue further vaccination was made by the subject's parent or guardian or the investigator and which of the following possible reasons was responsible for withdrawal:

- serious adverse event,
- non-serious adverse event,
- other (specify).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

10.2. Secondary endpoints

Efficacy during the first efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.

- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season.

Efficacy during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Efficacy during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in a subset of subjects, N=1800)

- Serum rotavirus IgA antibody concentration expressed as GMC at Visit 1 and Visit 3.
- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3. Refer to the glossary of terms for definition of seroconversion.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccines at Visit 3 and Visit 4 or Visit 6 (if applicable):
  - Serum concentration/titer expressed as GMC/Ts for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP, anti-HBs, anti-Men C or antibodies to the 7 *Streptococcus pneumoniae* serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-polio type 1 antibody titers ≥ 8
    - anti-polio type 2 antibody titers ≥ 8
    - anti-polio type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
    - anti-HBs antibody concentrations ≥ 10.0 mIU/ml
    - *Neisseria meningitidis* C serum bactericidal activity titer ≥ 1/8
    - ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 mcg/ml*** **(Amendment 1: 07 June 2005)**
    - antibody concentrations to *Streptococcus pneumoniae* serotypes 4, 9V,14, 18C, 23 F, 6B, 19F ≥ 0.05 mcg/ml
  - Seropositivity status:
    - anti-PT antibody concentrations ≥ 5 EL.U/ml
    - anti-FHA antibody concentrations ≥ 5 EL.U/ml
    - anti-PRN antibody concentrations ≥ 5 EL.U/ml

Safety and reactogenicity

- In a subset of subjects (N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccines.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccines, according to the MedDRA classification.

- For all subjects, occurrence of serious adverse events throughout the entire study period.

10.3. Estimated sample size

The primary objective of the study is to determine if two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations can prevent any RV GE caused by the circulating wild-type RV strains during the period starting from 2 weeks after Dose 2 of study vaccination until Visit 5 at the end of the first efficacy follow-up period.

3 990 subjects randomized to receive either the HRV vaccine or the placebo in a 2:1 ratio will be enrolled. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 3 390 subjects (2 260 in HRV and 1 130 in placebo groups respectively) are expected to be evaluable for the analysis of the primary objective.

Considering a 2:1 randomization ratio and various incidence rates, Table 12 provides the power that the 95% CI for vaccine efficacy be above given limits.

Results from a trial (Study 004) in Finland indicates that in placebo recipients an incidence rate of 10% for the percentage of subjects with any RV GE caused by the circulating wild-type RV strains from 2 weeks after Dose 2 of study vaccination up to Visit 5 at the end of the first efficacy follow-up period is a reasonable assumption.

Therefore if the vaccine efficacy is truly 70%, the study has at least 90% power to observe a 95% CI for the vaccine efficacy that will be above 50%.

Table 13 Power to observe a 95% CI above various cut-offs according to various incidence rates and true vaccine efficacy (power obtained from simulations using 2260 evaluable subjects in the HRV vaccine group and 1130 evaluable subjects in the placebo group) [see Appendix I for mathematical details]

Incidence rate in the placebo	True vaccine efficacy	Cut-off for the lower limit of the 95% CI on vaccine efficacy					
		0%	10%	20%	30%	40%	50%
Any Gastroenteritis							
10%*	70% 60%	100% 100%	100% 100%	100% 100%	100% 97%	100% 81%	91% 32%
8%	70% 60%	100% 100%	100% 100%	100% 99%	100% 94%	98% 73%	82% 29%
6%	70% 60%	100% 100%	100% 99%	100% 96%	99% 85%	93% 60%	71% 21%
Severe Gastroenteritis							
4%*	80% 70%	100% 100%	100% 99%	100% 98%	99% 93%	98% 81%	92% 53%
3%	80% 70%	100% 98%	99% 97%	99% 93%	97% 85%	93% 68%	80% 40%
2%	80% 70%	98% 92%	97% 86%	94% 78%	90% 64%	80% 46%	60% 26%

*anticipated incidence rate

A secondary objective is to explore the immunogenicity of the childhood vaccinations one month after the third dose of the primary vaccination course in each country. Two doses of the three-dose primary vaccination course would be co-administered with each dose of the HRV vaccine or placebo.

Using an estimation of the seroprotection rates of 97% for anti-diphtheria, of 99% for anti-tetanus, of 100% for anti-PRP, of 94% for anti-HBs, of 100% for anti-polio type 1, 2 and 3 antibodies and a standard deviation between 0.28 to 0.33 for anti-PT, anti-FHA, anti-PRN antibody concentrations (reference study: ROTA-007), and assuming that the rates / GMC are the same in the vaccine and placebo groups, a subset of 160 evaluable subjects in the vaccine group and 80 in the placebo group will provide at least 80% global power that all the 95% CIs on the decrease in seroprotection rates with the vaccine group as compared to the placebo group are below 10% and that the 95% CIs on the fold decrease in anti-PT, anti-FHA, anti-PRN GMCs with the vaccine group as compared to the placebo group is below 1.5 (using PASS 2000 for the difference in seroprotection rates and using Nquery for the ratio of anti-PT, anti-FHA, anti-PRN GMCs, one sided equivalence test, alpha=2.5%). These analyses will be exploratory.

Allowing for up to 20% of subjects who may not be evaluable for the immunogenicity analysis, a target total of 300 subjects will be sampled by country.

10.4. Study cohorts to be evaluated

Total Vaccinated cohort

The total vaccinated cohort will include all subjects with at least one vaccine administration documented:

- a safety analysis based on the total vaccinated cohort will include all vaccinated subjects,
- an immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects for whom immunogenicity data are available.
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available.

ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects:

- who received 2 doses of HRV vaccine or placebo,
- who have entered into the efficacy surveillance period:
  - have follow-up beyond 2 weeks after Dose 2 of study vaccination for the analysis of the first efficacy follow-up period,
  - have follow-up beyond the end of the first efficacy follow-up period for the analysis of the second efficacy follow-up period,

- have follow-up beyond 2 weeks after Dose 2 of study vaccination for analysis of the combined efficacy follow-up periods.

- for whom the randomization code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol

ATP cohort for safety

The ATP cohort for safety will include all vaccinated subjects

- who have received at least one dose of study vaccine/control according to their random assignment,
- for whom the randomization code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

ATP immunogenicity cohort

The ATP immunogenicity cohort will include all subjects from the ATP safety cohort:

- who have 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 comply with vaccination schedule for HRV vaccine or placebo,
- who comply with blood sampling schedule,
- for whom immunogenicity data are available, at pre and post sampling timepoint.
- who have no rotavirus other than vaccine strain in GE stool samples collected up to Visit 3.
- who have no concomitant infection unrelated to the vaccine which may influence the immune response.
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of dose 1. Refer to the glossary of terms for definition of seronegative.

The ATP efficacy cohort will be used for the primary analysis of efficacy. A secondary analysis of efficacy based on the total vaccinated cohort will also be performed.

The total vaccinated 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 ATP immunogenicity cohort will be used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort will only be performed if more than 5% of the enrolled subjects 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.

10.5. Derived and transformed data

Efficacy

An episode of GE will be classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain is identified in a stool sample collected during the episode. GE episode without stool sample/result available will not be considered in the analysis as a RV GE episode.

Reactogenicity

For a given dose, subjects with no symptoms (solicited or unsolicited) documented will be considered as subjects without symptoms (solicited or unsolicited).

Immunogenicity

The cut-off values of all antibodies are defined by the laboratory before the analysis and are described in Section 5.6.2.2.

A seronegative subject is a subject whose titer is below the cut-off value.

A seropositive subject is a subject whose titer is greater than or equal to the cut-off value.

Seroconversion is defined as the appearance of antibodies (i.e. titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination

The GMC calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

10.6. Final analyses

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed subsequently, and will be presented in an annex.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 5. However access to the individual treatment decode will be provided to the investigators only after the final analyses of the second efficacy follow-up be performed.

10.6.1. Analysis of demographics/baseline characteristics

The mean, range and standard deviation of height in cm, weight in kg and of age in weeks will be calculated per group. The racial and gender composition will be presented.

The distribution of subjects enrolled among the study centers will be tabulated as a whole and per group.

Summary of feeding criteria on the day of each study vaccination will be tabulated by group.

10.6.2. Analysis of efficacy

Vaccine efficacy will be calculated, with their 95% CI (see Appendix I for mathematical detail) against:

- any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any and severe RV GE due to G1 serotype caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any and severe RV GE due to non-G1 serotypes during the first efficacy follow-up period.
- hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any medical attention (medical provider contact, advice, visit; emergency room contact or visit; hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period for the subset of subjects who completed the two-dose vaccination course before the RV epidemic season.
- any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period for the subset of subjects who were vaccinated during the RV epidemic season.

The efficacy of the vaccine against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period will be first evaluated. The secondary efficacy objectives will be addressed using a hierarchical testing procedure according to the order listed above, provided that the primary efficacy objective has been reached.

In addition, vaccine efficacy against severe RV GE, severe RV GE due to G1 serotype, severe RV GE due to non-G1 serotypes, hospitalization due to RV GE and any medical attention for RV GE during the second efficacy period and on combined efficacy periods will be calculated, with their 95% CI.

Additional supportive and exploratory analyses will be performed (i.e. efficacy by country, efficacy against any RV GE during the second efficacy period, efficacy against

severe GE, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, efficacy against hospitalization due to GE of any etiology, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system and assessment of risk factors of RV infection).

10.6.3. Analysis of immunogenicity

In a subset of subjects (N=1800)

For each treatment group, at each time point that a given antigen is measured,

- Seropositivity/seroprotection /seroconversion rates and their exact 95% CI will be tabulated
- GMCs/GMTs and their 95% CI will be calculated.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 will be displayed using reverse cumulative curves.

The asymptotic standardized 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between vaccine and placebo groups will be computed.

In addition, for all childhood vaccinations co-administered with each study vaccine dose, the distribution of antibody titers after the second (if applicable) and one month after the third dose of the childhood vaccinations will be displayed, per country, using reverse cumulative curves.

Difference between vaccine and placebo groups after the second (if applicable) and one month after the third dose of the routine primary vaccination course will be evaluated per country with respect to immune response to the childhood vaccines:

- The asymptotic standardized two-sided 95% CI for difference in seropositivity/seroprotection rates between vaccine and placebo groups will be calculated.
- The two-sided 95% CI for the ratio of GMCs/GMTs between vaccine and placebo groups will be computed (using a one-way ANOVA model on the logarithm10 transformation of the titers).

10.6.4. Analysis of safety

In a subset of subjects (N=1800)

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 dose, for overall doses and per subject.

The incidence, with exact 95% CI, of each individual solicited general symptom, will be calculated by group, over the solicited follow-up period, after each dose, for all doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

An increase in the incidence of specific symptoms in HRV vaccine group as compared to placebo group will be explored using two-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 also be performed.

For all subjects

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA, the Medical Dictionary for Regulatory Activities. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited symptoms occurring within 31 days with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited symptoms with relationship to vaccination.

Serious adverse events reported during the study period will be summarized by group.

10.7. Planned interim analysis

(Amendment 1: 07 June 2005)

In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on subjects ***from the Czech Republic and Finland only*** from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data ***on solicited and unsolicited symptoms,*** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. ***No*** study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.

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

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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 fulfilment 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)

1. 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)

2. 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 and equipment 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 GSK Biologicals 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 ensure that no clinical samples (including serum samples) are retained on site or elsewhere without the approval of GSK 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 co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation; administrative changes are submitted to IRBs/IECs for information only.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such

action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to the investigational site.

V. Monitoring by GSK Biologicals

Monitoring visits by a professional representative of the sponsor will be scheduled to take place as close as possible to entry of the first subject, during the study at appropriate intervals and after the last subject has completed the study. It is anticipated that monitoring visits will occur at a frequency defined before study start.

These visits are for the purpose of confirming that GSK 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 accuracy of data entered on the RDE screens and Vaccine Inventory Forms. The monitor will verify 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 RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK 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 agencies and GSK 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, Biologics Licensing Application.

GSK Biologicals has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of vaccine development. GSK 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 GSK Biologicals sponsored studies are in accordance with GCP 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 GSK Biologicals' audits entail review of source documents supporting the adequacy and accuracy of eCRFs, review of documentation required to be maintained, and checks on vaccine accountability. The GSK Biologicals' audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK 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 consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of eCRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next

paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed Publication. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

APPENDIX C OVERVIEW OF THE RECRUITMENT PLAN

- The study will be conducted multiple sites in six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain).
- Target enrollment will be 3990 eligible subjects.
- A total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.
- Recruitment will be terminated when 3990 eligible subjects have been enrolled.
- All subjects will be enrolled within a period of 4 months.
- ***Recruitment was terminated on 31 January 31 2005.*** **(Amendment 1: 07 June 2005)**
- Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per subject, will not exceed a total of maximum of 24 months.
- The recruitment will be monitored by the site monitor / SBIR.

APPENDIX D HANDLING OF BIOLOGICAL SAMPLES COLLECTED BY THE INVESTIGATOR

Instructions for Handling of Serum Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

3. 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 to minimize the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

4. Serum separation

These guidelines aim to ensure high quality serum by minimizing the risk of haemolysis, 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 ten 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 tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.
- 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 label provided by GSK Biologicals (see point 3).

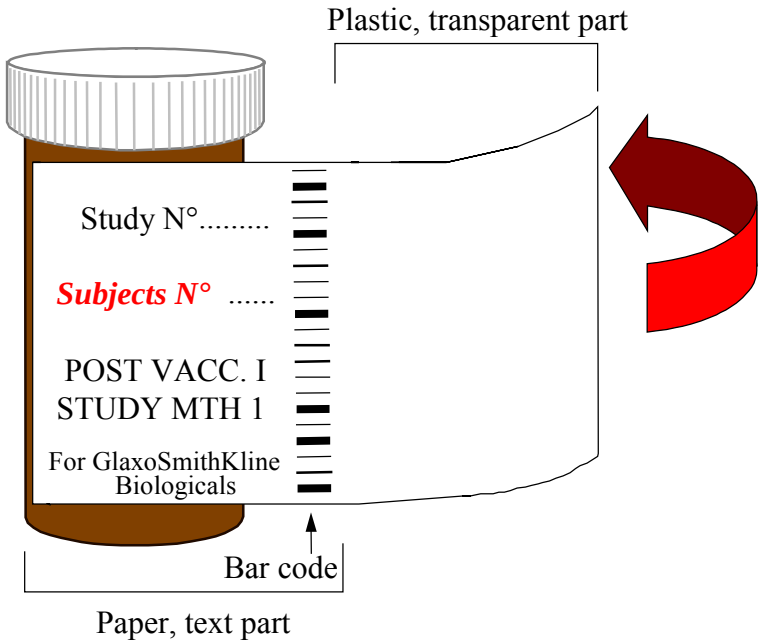
5. Labelling

- The standard labels provided by GSK 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.

(Amendment 1: 07 June 2005)



- Labels should not be attached to caps.

6. Sorting and storage

- Tubes should be placed in the GSK Biologicals' cardboard boxes 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 approximately -20°C (alternatively at approximately -70°/80°C is also acceptable) until shipment to GSK Biologicals. The storage temperature should be checked regularly and documented. Wherever possible, a backup facility for storage of serum samples should be available.
- A standard Serum Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. 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 serum samples.

- Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.[1]

GLAXOSMITHKLINE BIOLOGICALS

Attention Biospecimen Reception
Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart – Belgium
Telephone: [redacted] or [redacted]
or [redacted] or [redacted]
Fax: [redacted]
E-mail: [redacted]

Instructions for Handling of Stool Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

- Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any gastroenteritis episodes. Parents/guardians will be asked to preferably use the containers to collect stool samples. If this is not possible, soiled diapers should be individually placed in the ziplock bags and sealed.

2. Labelling

- The parents/guardians/study personnel should complete the label provided on the container/ziplock bag label with a black ink or ballpoint pen and return the collected stool samples to the study personnel.
- If necessary, any hand-written additions to the labels by the study personnel should be made using indelible ink.

3. Sorting and storage

[1] The Serum Listing Form and the Specimen Transfer Form are standard documents used in GSK Biologicals' clinical trials. These documents are provided by GSK Biologicals' Clinical Trials' monitor at study initiation.

- The 8 ml tubes with stool specimens should be stored at a temperature between -20°C and -70°C until shipment to GSK Biologicals. Wherever possible, a backup facility for storage of stool samples should be available
- A standard Stool Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. 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 serum samples.
- Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.[2]

Please refer to the GSK contact information mentioned above for serum samples.

Instructions for Handling of Biological Samples collected during IS

When materials are provided by GSK Biologicals, it is mandatory that all clinical samples (including serum samples) be collected and stored 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.

All biological specimens should be labelled to allow sample identification. If necessary, any hand-written additions to the labels should be made using indelible ink.

For samples to be tested locally at the investigator's laboratory

- Fresh stool samples should be maintained at the investigator's laboratory for testing for the presence of enteric pathogens such as Salmonella, Shigella, Campylobacter, E. coli and Yersinia.

For samples to be shipped to GSK Biologicals, Belgium

- The stool samples should be aliquoted in two samples, placed in 8 ml tubes and be kept at –20°C to –70°C. Rectal swabs and throat swabs should be placed in sterile transport media and frozen at –20°C to –70°C until shipment to GSK Biologicals. Acute and convalescent sera should be stored at –20°C until shipment to GSK Biologicals. If applicable, surgical specimens should be washed, stored and shipped according to the instructions in the lab workbook. Wherever possible, a backup facility for storage of stool samples should be available.

A standard Specimen Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. 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 stool samples.

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[2] The Stool Listing Form and the Specimen Transfer Form are standard documents used in GSK Biologicals' clinical trials. These documents are provided by GSK Biologicals' Clinical Trials' monitor at study initiation.

Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.

Please refer to the GSK contact information mentioned above for serum samples.

APPENDIX E SHIPMENT OF BIOLOGICAL SAMPLES

Instructions for Shipment of all Biological Samples

Biological samples should be sent to GSK Biologicals at regular intervals. The frequency of shipment of samples should be decided upon by the Site Monitor, Central Study Coordinator and the investigator prior to the study start.

Biological samples should always be sent by air, preferably on a Monday, Tuesday or Wednesday, unless otherwise requested by the sponsor.

Biological samples (except IS surgical samples) must be placed with dry ice (maximum -20°C) in a container complying with International Air Transport Association (IATA) requirements. The completed standard biological samples listing form should always accompany the shipment.

The container must be clearly identified with the labels provided by GSK Biologicals specifying the shipment address and the storage temperature (-20°C or 2-8°C for IS surgical samples).

The airway bill should contain the instruction for storage of samples at maximum -20°C or 2-8°C for IS surgical samples.

A "proforma" invoice, stating a value for customs purposes only, should be prepared and attached to the container. This document should contain the instruction for storage of samples at maximum -20°C or 2-8°C for IS surgical samples.

Details of the shipment, including:

* number of samples
* airway bill
* flight number
* flight departure and arrival times

should be sent by fax or by e-mail, two days before shipment, to:

GLAXOSMITHKLINE BIOLOGICALS
Attention Biospecimen Reception
Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart – Belgium
Telephone: [redacted] or [redacted]
or [redacted] or [redacted]
Fax: [redacted]
E-mail: [redacted]

APPENDIX F LABORATORY ASSAYS

Description of Clinical Immunological Assays

Measurement of IgA Antibodies by ELISA

This assay allows the detection of rotavirus IgA in human serum and was initially designed by [redacted] (1, 2) and has been adapted by GSK Biologicals. It will be used for measuring the immune response after vaccination and/or infection. Samples will be analyzed at GSK Biologicals, Rixensart, Belgium (or designated laboratory).

Description of the ELISA Assay

96-well plates are coated by overnight incubation with anti-rotavirus antibody dilutions. The wells are washed and a lysate of cells either infected with vaccine strain (positive wells) or either uninfected (negative wells) is added. Following incubation on a rotating platform, the plates are washed and the dilutions of serum samples or standard serum are incubated in both kinds of wells (positive and negative). The use of negative wells allows the assessment of non-specific IgA binding.

The plates are washed and bound human IgA is detected by addition of biotinylated rabbit anti-human IgA (30 minutes under agitation). After washing the plates, peroxidase-conjugated avidin-biotin at an optimal concentration is added to each well and incubated (30 minutes, RT under agitation). Plates are again washed and orthophenylenediamine (OPD) is added. The plates are then incubated (30 minutes, room temperature (RT) in darkness) before the reaction is stopped with 2N H2SO4.

Optical absorption is measured at 490/620 nm. Specific optical densities are calculated for each sample / standard by measuring the difference between positive and negative wells. Concentrations of the samples are determined by using the four-parameter logistic function generated by the standard curve. The most accurate part of the standard curve (working range) for the calculation of the results is determined. Antibody concentrations in units per milliliter (U/ml) are calculated 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 corrected for the dilution factor. Each experiment includes negative and positive controls.

For all reagents optimal concentration are pre-determined.

References

1. 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.

2. 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.

Stool assays

1. Antigen Detection in Stool Samples

Rotavirus antigen in stool samples collected during gastroenteritis episodes will be detected by ELISA at Central Lab (GSK or designated laboratory).

2. RV strain typing

Targeted RV gene will be amplified by Reverse Transcriptase Polymerase Reactions (RT-PCR) to generate RV cDNA fragments. The genotype will be confirmed by hybridization using serotype-specific DNA probes and/or by direct sequencing of the amplified RV cDNA product.

This serotyping analysis can be completed with the determination of the P-serotype which is related to the VP4 gene. In that case, the typing approaches will be based on the methods such as described for the G typing.

APPENDIX G VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY

1. Vaccine and/or other supplies

GSK Biologicals will supply the following amounts of numbered doses of study vaccine, sufficient to administer 2 dose(s) to all subjects as described in the present protocol.

- 5320 doses of the HRV vaccine in monodose vials.
- 2660 doses of the placebo in monodose vials.
- 7980 doses of the diluent (calcium carbonate buffer) pre-filled syringes.

An additional 5% of their respective amounts will be supplied for replacement in case of breakage, bad storage conditions or any other reason that would make the vaccine unusable (i.e. given by mistake to another subject). An additional quantity of vaccine stock not exceeding 20% of their respective amounts will be provided in order to allow over randomisation.

Commercially available lots will be provided for Infanrix Hexa®, Infanrix Polio Hib® and ***Prevenar*®** by GSK Biologicals, Rixensart, Belgium. **(Amendment 1: 07 June 2005)**

All monodose vials/pre-filled syringes must be accounted for on the form provided.

Labels for sample identification:
The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each timepoint. Each label will contain the following information: study number, identification number for the subject, sampling timepoint , timing , biological specimen (e.g. serum / GE stool).

Other supplies provided by GSK Biologicals:
In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:
For example:

- material for biological specimen during IS,
- material for blood collection,
- material for stool samples.

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers,

when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site

On arrival of vaccine shipment, the ***cold chain monitoring device*** should be removed from the vaccine boxes and checked. The temperature recording chart (chart from Cox recorder or print-out data of the electronic device) should be obtained from the temperature recording device. **(Amendment 1: 07 June 2005)**

The following documents should be completed and returned to GSK Biologicals on reception of vaccine shipment:

Notification of vaccine delivery/temperature control
Copy of the temperature recording (chart).

These documents should then be returned to:

(Amendment 1: 07 June 2005)

Attention of ***Clinical Trials Supply Unit***
Clinical Operations Logistics
GSK Biologicals Rixensart
Fax : [redacted]
E-mail: [redacted]

In case of any temperature deviation, the official approval for the use of vaccine must be obtained from GSK Biologicals.

4. Vaccine accountability

At all times 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 used and unused stocks. An explanation must be given of any discrepancies.

After approval from GSK Biologicals and in accordance with GSK SOP-WWD-1102, used and unused vaccine vials/syringes/containers should be destroyed at the study site using locally approved biosafety procedures and documentation unless otherwise described in the protocol. If no adequate biosafety procedures are available at the study site, the used and unused vaccine vials/syringes/containers are to be returned to an appropriate GSK Biologicals site for destruction, also in accordance with current GSK SOP-WWD-1102.

5. Transfers of clinical vaccines or products from country medical department or dispatch centre to study sites or between sites

Storage temperatures must be maintained during transport and deviations must be reported to Clinical Operations Logistics for guidance. All transfers of clinical vaccines or products must be documented using the Clinical Supply Transfer Form.

All packaging and shipment procedures for transfer of clinical vaccines or products must follow procedures approved by the sponsor.

Clinical vaccines or products should always be sent by contract courier designated by the sponsor, unless otherwise requested by the sponsor.

Alternative local validated procedures may be followed after the documentation for these procedures has been sent to Clinical Operations Logistics and approval has then been obtained from the qualified person (or designee) in GSK Biologicals, Rixensart, before any shipment of vaccines.

APPENDIX H 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 GSK Contact for Serious Adverse Event (SAE) Reporting.

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, collection date and process of serum, throat , stool and surgical specimen if any as well as any other information thought necessary for assessment by the study staff should be reported to the GSK safety contact by using the IS reporting form.

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 a range of suspected pathogens including Salmonella, Shigella, Campylobacter, and Yersinia. 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 GSK Biologicals, such as virus culture, antigen detection by immunoassay, or electron microscopy for virus-like particles. Accordingly, a complete set of stool specimens (collected just prior to or immediately after the air or contrast enema, 24 hours and 48 hours after the reduction) will be comprised of 3 specimens submitted for bacterial culture and 6 frozen specimens retained for shipment to GSK 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.

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.

In case of surgical resection, 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. As molecular assays are to be performed on these surgical specimens, the use of powderless gloves, RNAse-free pipettes, aerosol RNAse-free tips, non-autoclaved disposable plasticware/forceps, commercial PBS solution/ water/ formaldehyde solutions as well as limited steps of the solution preparation are highly recommended to avoid RNAse contamination. Refer to the lab workbook for the process of resected tissue. A broad range of tests including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR and other tests will be arranged by GSK Biologicals in consultation with the Attending Pathologist.

Acute and convalescent blood (at least 2 ml of each) should be collected. Serum should be 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 GSK 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 I MATHEMATICAL DETAILS ABOUT SAMPLE SIZE DETERMINATION SHEET

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{rn2}$$

where n1 = number of cases in the vaccine group

N1 = number of subjects in the vaccine group

n2 = number of cases in the placebo group

N2 = number of subjects in the placebo group

N1/N2 = r

*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 binomial 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.

(Amendment 1: 07 June 2005)

APPENDIX J FRENCH ADMINISTRATIVE CONSIDERATIONS

This appendix includes all the requirements of the French law (n°88-1138 of 20 December 1988 modified), and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « STUDY POPULATION»

- ***In line with the local regulatory requirements, the following text about « NATIONAL FILE » is added :***

All subjects participating in studies could be identified and monitored under the « Fichier national ».

The following details will be described:

- ***first 3 letters of name and first 2 letters of surname,***
- ***date of birth,***
- ***reference of the study and dates of beginning and termination,***
- ***exclusion period,***
- ***the total amount of honorarium.***

- ***In line with the local regulatory requirements, the following text in section «OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS » is added :***

A subject will be eligible for inclusion in this study if he /her is either affiliated to or beneficiary of a social security category.

It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

- ***In line with the local regulatory requirements, the following text about «PAYMENT TO SUBJECTS » is added :***

Subjects could be paid (if applicable) for the inconvenience of participating in the study. The amount of payment is stated in the informed consent form. Subjects not completing the study for whatever reason could be paid at the discretion of the Investigator, generally on a <u>pro rata</u> basis.

2. Concerning the " DATA ANALYSIS AND STATISTICAL CONSIDERATIONS " and specially in the " SAMPLE SIZE ASSUMPTION "

The expected number of patients to be recruited in France is declared to the French regulatory authority and is included in the Patient Informed Consent Form.

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

- ***In section " Regulatory and Ethical Considerations, Including the Informed Consent Process"***

  – ***Concerning the process for informing the patient or his/her legally authorized representative, the following text is added :***

  French Patient Informed Consent form is a document in triplicate which summarizes the main features of the study and allows collection of the patient's written consent. It also contains a reference to the advice from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.

  – ***Concerning the process for obtaining subject informed consent,***

  If the patient is under 18 years old, the following text is added (if applicable):

  The consent of the child will be also sought when he/she is old enough to express his/her opinion. His/her refusal or the revocation of his/her consent cannot be disregarded. If only one holder of parental authority signed the consent form, the investigator will ask the present person to file, date and sign and affidavit (in triplicate) indicating wich his situation regarding the parental authority. A copy of this affidavit is joined to each consent form.

  If these directives are not followed, the patient inclusion could be considered as a protocol violation and the data of this case won't be taken into account.

  – ***Concerning the management of the Patient Informed Consent forms, the following text is added :***

  The first copy of the Patient Informed Consent form is kept by the Director of the Medical Department of GlaxoSmithKline France. The second copy is kept by the investigator and the last copy is given to the patient or his/her legally authorized representative.

  The first copy of all the consent forms will be collected by the investigator at the end of the trial under the Clinical Research Assistant's (CRA's) control, and placed in a sealed envelope bearing only :

  - ***the study number,***
  - ***the identification of the Centre : name of the principal investigator and number of center),***
  - ***the number of informed consents,***
  - ***the date,***
  - ***and the principal investigator's signing.***

Then, the CRA hands the sealed envelope over to the Director of the Medical Department, for confidential recording, under his responsibility.

- ***In section concerning the " NOTIFICATION TO THE HOSPITAL DIRECTOR " the following text is added (if applicable)***

In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.5121-17).

- ***In section concerning the " INFORMATION TO THE HOSPITAL PHARMACIST " the following text is added (if applicable)***

In accordance with Article R.5121-18 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

- ***In section " RECORDS RETENTION "***

Concerning the documents to be retained by the Investigator is added :

The correspondance with the French Ethic committee must be filed only by the "Coordinating Investigator".

- ***In section " DATA MANAGEMENT " the following text is added***

" within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by Laboratoire GlaxoSmithKline or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through Laboratoire GlaxoSmithKline (Clinical Operations Department)."

" dans le cadre de cet essai clinique, les données concernant l'identité des investigateurs et/ou des co-investigateurs et/ou du pharmacien si applicable, participant à cet essai clinique, et les données concernant les patients recrutés dans cet essai clinique (numéro patient, numéro de traitement, statut du patient eu égard à l'essai clinique, dates de visites, données de santé) seront collectées et intégrées dans les bases de données GSK par Laboratoire GlaxoSmithKline ou pour son compte, pour le suivi, la gestion de l'essai clinique et l'utilisation des résultats de celle-ci. Conformément à la loi n° 78-17 du 6 janvier 1978 modifiée, chacune desdites personnes a un droit d'accès, de correction et d'opposition sur ses propres données par le biais de Laboratoire GlaxoSmithKline (département Opérations Cliniques)."

4. Concerning the « SAE »

In section " TRANSMISSION OF THE SAE REPORTS " :

The SAE Reports have to be transmitted to the GSK France Drug Safety Department, which name, address and phone number are :

Département de Pharmacovigilance

Laboratoire GlaxoSmithKline

100 Route de Versailles

78163 MARLY LE ROI

Tel : [redacted]

Fax : [redacted]

Attachment 1 Study Contacts for Reporting SAEs

This section is NOT a part of the protocol, but is a separate element of the study package.

(Amendment 1: 07 June 2005)

Czech Republic	The Safety Team GSK (Medical Department Vaccines for Central and Eastern Europe), Na Pankraci 17/1685, 140 21 Praha 4, Czech Rep Tel: [redacted] or [redacted] Fax: [redacted] Email: [redacted]
Finland	[redacted] Manager Pharmacovigilance and Medical Information, GSK Finland, Box 24 02231 Espoo, Finland Tel: [redacted] Fax: [redacted] Email: [redacted]
	From 06 Augist 2005 [redacted] ***GlaxoSmithKline*** ***PO Box 24 (Piispansilta 9A), 02231 Espoo, Finland*** ***Tel:*** [redacted] ***Fax:*** [redacted] ***(Backup:*** [redacted] ***Mobile:*** [redacted] ***e-mail:*** [redacted]
France	[redacted] Adjoint de Pharmacovigilance 100, route de Versailles, 78163 Marly le Roi Cedex, France Tel: [redacted] Fax: [redacted]
Germany	[redacted] GlaxoSmithKline GmbH & Co. KG Theresienhoehe 11 80339 Munich, Germany Tel: [redacted] Fax: [redacted] email: [redacted]
Italy	Dr [redacted] Drug Surveillance, GlaxoSmithKline Italy, Via A. Fleming, 2, 37135 Verona – Italy Tel: [redacted] Fax: [redacted] email: [redacted]
Spain	[redacted] Head of Pharmacovigilance Spain C/Severo Ochoa 2, 28760 Tres

Cantos Madria, Spain
Tel: [redacted]
Fax: [redacted]
Mobile: [redacted]

GlaxoSmithKline Biologicals
Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment date:	**Amendment 1 – 07 June 2005**
Coordinating author:	[redacted] Scientific Writer

Rationale/background for changes: This protocol was amended on **07 June 2005** for the following reasons:

- Specify measurement of anti Neisseria meningitidis antibody concentrations by ELISA for subset from Spain.
- Specify details of the reactogenicity interim analysis.
- To implement administrative changes (update SAE contact information, study contact information, sponsor information).
- Implement minor corrections/clarifications.

The following strikethrough and bolded italic text were amended:

Title page

Contributing authors [redacted] ~~Director~~

[redacted] ***Clinical Development Manager***

Sponsor signatory: [redacted] ~~Director~~

[redacted] ***Director***

Synopsis (Study design), Section 3 and Section 5.2

Finland: 3, 5, ***11***-12 months

- Study visits: Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 6).

  Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** ~~will~~ have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines.

Section 3

*At 7 months of age only for subjects from Spain ***(optional)***.
#At 12 months of age only for subjects from Italy ***(optional)***. At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" ***(optional)***.

Synopsis (Secondary Endpoints) and Section 10.2

- ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 mcg/ml***

Section 5.2

- In addition, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" (target N=300 per country) ~~will~~ ***may*** have ***if necessary*** an additional study visit because the blood sampling timepoint one month post Dose 3 of the childhood vaccines in these countries does not ***always*** coincide with study visits planned for all subjects.

Section 5.4 (Table 1)

Age **Visit** **Timing** **Sampling timepoint**	**6-14 weeks** **VISIT 1** **Day 0** **Pre**	**VISIT 2** **Month 1 or 2**	**VISIT 3** **Month 3 or 4** **Post vacc 2**	**VISIT 5**	**VISIT 7**
Physical examination	●	●	●‡		
Recording all childhood vaccinations	●	●	●	● ***Finland/Italy only***	
Record any concomitant medication/vaccination#	●	●	●	●	~~●~~

§Additional visits ***can be*** ~~are~~ planned ***if necessary*** for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset":

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 2)

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2*	VISIT 6 ITALY only Month 9 Post-vacc 2*	 FINLAND only Month 10 Post-vacc 2*
Physical examination	•‡	•‡	•‡

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 3)

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine schedule	3, 4, 5 months	3, 5, *11*-12 months	2, 3, 4 months	3, 5, 11 months	2, 4, 6 months

Section 5.5

Visit 4 is optional and may be combined with Visit 5.

Visit 6 is optional and may be combined with Visit 5.

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)***

Section 5.6.2.2

In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity ***and ELISA test***, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Table 5 Laboratory Assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	***In-house***	***mcg/ml***	***0.3***

Section 5.6.4

Table 6 Serology and Stool Analysis Plan

Serology					
Post-vacc 2∗	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP, 7 *S. pneumoniae* serotypes (France and Germany only)	Immunogenicity subset ***except Spain*** (N=1~~5~~800)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), ~~serum bactericidal activity (Spain only),~~ D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	***3***	***HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)***	***N=300 from Spain***	***HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.***
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity ***and ELISA test***	N=300 from Spain	***Men C*** serum bactericidal activity ***and ELISA test***, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Section 6.1

GSK Biologicals' Infanrix Hexa®, Infanrix Polio Hib® ***and Prevenar®*** vaccines will be also supplied.

~~Prevenar® and Meningitec® if to be used during the study should be bought locally.~~

Section 6.3

All vaccines must be stored in a safe and locked place with no access for unauthorized personnel.

Vaccines will be stored at the defined range of temperature (i.e. +2 to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of temperature deviation (temperature outside the defined range, i.e. +2 to +8°C/ 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

proper functioning was demonstrated during the monitor's site evaluation,

if the system continues to work in case of a power failure, and

if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working when after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag®) close to the vaccines as a back up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C/ 36°F to 46°F), must be reported within 24 hours to the Sponsor (i.e. Study Monitor/ GSK Local Contact/ GSK Biologicals)

Following exposure to a temperature deviation, vaccines will not be used until written approval is given by the sponsor.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.

~~All vaccines 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/ 36°F to 46°F) and must not be frozen. Storage temperature should be monitored and documented at least once per day. Monitors will check the record chart at least once per month or after any out of range storage. It is advisable to have a back-up refrigerator/ freezer in case of power failure/ breakdown. Procedures must be in place to ensure that the vaccine is kept at the indicated temperature range at all times.~~

~~The study monitor must be contacted, as soon as possible, if the cold chain is broken (e.g. vaccines become frozen or refrigeration fails).~~

~~Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.~~

Section 8.8.2

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician ~~Dr~~ [redacted] Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [redacted] ***or*** [redacted]

Section 10.6.2

Additional supportive and exploratory analyses will be performed (i.e. efficacy by country, efficacy against any RV GE during the second efficacy period, efficacy against severe GE, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, efficacy against hospitalization due to GE of any etiology, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system and assessment of risk factors of RV infection).

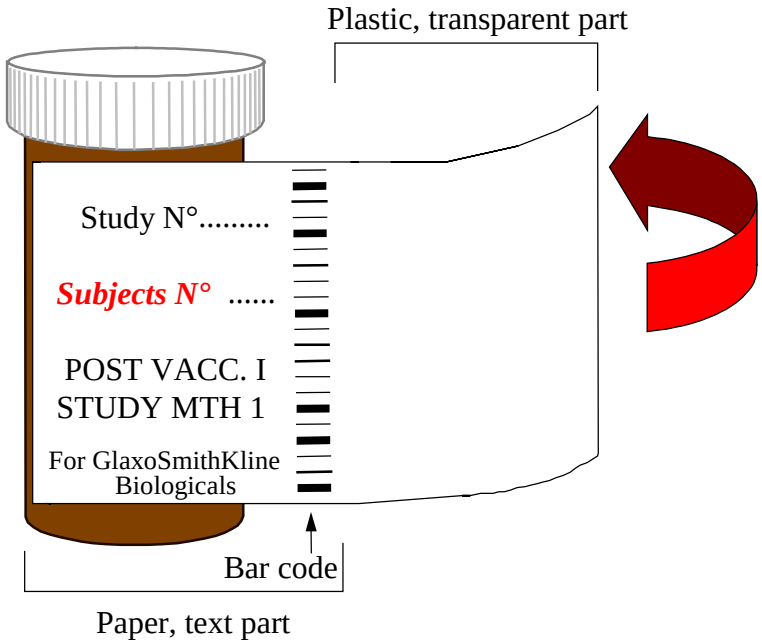
Section 10.7

In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on ~~all~~ subjects ***from the Czech Republic and Finland only*** from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data ***on solicited and unsolicited symptoms,*** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. ***No*** study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.

Appendix C

- Recruitment was terminated on 31 January 31 2005.

Appendix D



4. Collection

Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any ~~severe~~ gastroenteritis episodes.

Appendix G

Commercially available lots will be provided for Infanrix Hexa®, Infanrix Polio Hib® and ***Prevenar®*** by GSK Biologicals, Rixensart, Belgium.

~~Prevenar® and Meningitec® vaccines will be obtained locally.~~

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site

On arrival of vaccine shipment, the ~~freeze indicator~~ ***cold chain monitoring device*** should be removed from the vaccine boxes and checked ~~after 10 minutes at room temperature~~.

Attention of ***Clinical Trials Supply Unit*** [redacted]
E-mail: [redacted]

Appendix J

Appendix J FRENCH ADMINISTRATIVE CONSIDERATIONS was added.

Attachment 1 and Attachment 2

Study contact information and sponsor updated as appropriate.

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Approved by: Director, Clinical Development	[redacted] dd-mm-yyyy

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
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Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	 _____ _____

GlaxoSmithKline Biologicals

Study Title A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

File Note to Study 102247 (Rota-036) Protocol Amendment 1 dated 07 June 2005

Reason for File Note: This file note is issued to clarify formatting errors noted in the 102247 (Rota-036) Protocol Amendment 1 dated 07 June 2005.

- There are two instances, one on page 44 (Section 4.5) and one on page 87 (Section 9.2), where "Section 0" is referenced. The correct reference in both instances should be to Section 8.7.
- Protocol Appendix D on page 109 begins with Section 3. The correct numbering for items under the "Instructions for Handling of Serum Samples" should begin at "1".

These formatting errors had no impact on the content of the protocol.

Prepared by:

Scientific Writer: [redacted] 26Apr/2007
(dd-mm-yy)

CONFIDENTIAL 102247
Final

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Date of approval	Final 11 June 2004
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Sponsor signatory approval

Sponsor signatory: [redacted] Director

Signature: [redacted]

Date: 15 Jun 2004

Investigator Agreement

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
Title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), prescribing information (in the case of a marketed vaccine) and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine).
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investig[redacted] 23 JUNE 2004

Date

Study 102247 (ROTA-036)

FILE NOTE – 15 March 2006

Concerns Original Final Protocol 11 June 2004 - Co-Investigators signatures pages
Amendment 1 - 07 June 2005 Co-Investigators signatures pages
CZEC REPUBLIC

- Study Protocol finalized 11-June-2004 was signed by Prof. [redacted] (Principal Investigator) on June, 23th 2004.
- Amendment 1 issued 07-June-2005 was signed by Prof. [redacted] (Principal Investigator) on July, 13th 2005.

The Co-Investigators did not sign the Final Protocol and the Amendment 1 as Prof. [redacted] was the Co-ordinating PI.

[redacted]
(Central Study Coordinator)

Date: 15 MAR 2006.

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Prof. [redacted]

[redacted] 22 June 2004

Investigator signature **Date**

NOTE TO FILE

Study: **102247 (rota-036 - Europe)**

Site #: **FINLAND** [redacted]

ITEM: **Signing of Final Protocol and Amendment #1**

Study 102247 (Rota-036 – Europe) study protocol was finalised 11-Jun-2004. Amendment #1 was issued 07-Jun-2005. At following centers in Finland there has been a change in the principal investigator (PI) between study start / final protocol (FP) and Amendment #1 (AM#1). Amendment #1 has been approved by local CA (National Agency for Medicines) on 28-Jul-2005. Following is to clarify the signing of the Protocol Investigator Agreement / Amendment approval pages at five centers:

[redacted]
- former PI [redacted] end date: 19 Apr 2005 – has signed FP
- new PI [redacted] - has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 03 Apr 2005 – has signed FP
- new PI [redacted] - has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 30 Jun 2005 – has signed FP
- new PI [redacted] - has signed AM#1

[redacted]
- former PI [redacted] end date: 30 Sep 2005 – has signed FP
- new PI [redacted] - has signed AM#1

[redacted]
- former PI [redacted] end date: 27 May 2005 – has signed FP
- new PI [redacted] - has signed FP and AM#1

Signature and date:

27 Jan 2006

[redacted]

[redacted]

Clinical Trials Manager
GlaxoSmithKline, Espoo, Finland

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 08 SEP 2007

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 06 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigat[redacted]

09SEP2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]ure

05-oct-04

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 02 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]
Investigator signature

04 may 2005
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

6. SEP. 2007
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 09-SEP-2009

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 07 Sep 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 2.9.2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04 oct 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04 MAY 2005

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Inv [redacted]

08 Sep 2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 09Sep2004

Investigator **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 10SEP2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]re

17SEP2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

13 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

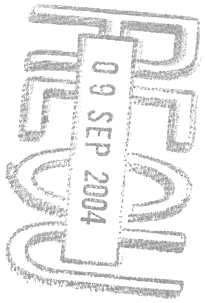
Inves [redacted] **Date** 08.03.2007

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

6-09-04

Investigator signature **Date**



- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator sig [redacted] **Date** 6-9-04

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted] **Date** 9.9.2004

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted]

Date 6 9 07

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted]

Date 9 Oct

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator si [redacted] 11/10/04

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator s[redacted] **Date** 150904

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 16/9/04

Investigator signature **Date**

[redacted]

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 06.09.04

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

06/09/2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signat [redacted]

06 29 06

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investiga [redacted] **Date** 9/9/04

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04/09/05

Investigator signature **Date**

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature [redacted] **Date** 4 September 2007

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signat [redacted] **Date** 03 09 04

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 17.09.04

Investigator signature **Date**

France [redacted]

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 13/09/04

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

16/09/2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator si [redacted] **Date** 300904

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator [redacted] **Date** 7/10/2004

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

13 03 04

Date

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signatur [redacted]

E9/09/04

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature **Date**

10-10-04.

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator sig [redacted] **Date** 13/10/04

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signatur **Date** 20/10/04

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

In [redacted]

21.10.2009
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signatu [redacted] **Date** 26.10.04

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22.09.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med. [redacted]

Investigato [redacted] 25. Aug. 04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 07.10.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted]

Investigator

25 AUG 2004

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted] 24. Sept. 04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

13.10.04
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents

Investigator name: Dr. med. [redacted]

Investigator signat[redacted] 23.08.04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 28.9.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents

Investigator name: Dr. [redacted]

[redacted] 23.08.2004

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 23.8.04

Investigator **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22.9.04

Investi **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Co – **Investigator name:** [redacted]

[redacted] 23/08/04
Investigator **Date**

[redacted] 06/09/04

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004
LKP signature **Date**

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 06/09/2004

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Prof. Dr. [redacted]

[redacted] 26.8.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 26.08.2004

Date

[redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investi

25-AUG-2004
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med. [redacted]

[redacted] 23. Aug. 2004

Investigator signature [redacted] **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted]
Investigator signature

21.10.04
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]
LKP signature

23.06.2004
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Investigator signature [redacted] 28.10.2004 **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 12.09.04

Investi **Date**

[redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22 SEP 2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 01 FEB 2005

Investigator signature **Date**

[redacted]

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 27.05.2005

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 23804

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 23.05.07

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: DR [redacted]

[redacted] 21 of OK

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 29.08.04

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator na Dr. med. [redacted]

Investigator si [redacted] 30 AUG 2004 **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med. [redacted]

[redacted]

Investigator signature

7/11/04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
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Investigator name: [redacted]

Investigator [redacted] 27 08 04 **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: Dr. [redacted]

[redacted]

Investigat 23/08/04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature 23.06.2004

Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 24.08.04

Investigator **Date**

[redacted]

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted] Dr. med [redacted]

[redacted] 23-09-2004

Investigator signature **Date**

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

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Investigator name: [redacted]

[redacted]

Investigator signature

Oct 8th 2004

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

LKP signature

23.06.2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. [redacted]

[redacted] 28.5.04

Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted] 23.06.2004

LKP signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr. med [redacted]

[redacted]

Investiga

10. Okt. 2004
Date

[For Germany only]

"Leiter der klinischen Prüfung" (LKP) name: Dr. med. habil. [redacted]

[redacted]

23. 06. 2004
Date

LKP signature

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 04/11/2004

Investigator signature **Date**

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Inve[redacted] **Date** 27/OCT/04

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

04/NOV/2004

Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: DR. [redacted]

[redacted]

26/10/07
Date

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

Invest [redacted] **Date** 17/11/2009

GlaxoSmithKline Biologicals Clinical Research & Development Protocol Amendment Approval	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment date:	**Amendment 1 – 07 June 2005**
Coordinating author:	[redacted] Scientific Writer
Rationale/background for changes: This protocol was amended on **07 June 2005** for the following reasons: • Specify measurement of anti Neisseria meningitidis antibody concentrations by ELISA for subset from Spain. • Specify details of the reactogenicity interim analysis. • To implement administrative changes (update SAE contact information, study contact information, sponsor information). • Implement minor corrections/clarifications.	

The following strikethrough and bolded italic text were amended:

Title page

Contributing authors [redacted] ~~Director~~

[redacted] ***Clinical Development Manager***

Sponsor signatory: [redacted] ~~Director~~

[redacted] ***Director***

Synopsis (Study design), Section 3 and Section 5.2

Finland: 3, 5, ***11***-12 months

- Study visits: Subjects from the "immunogenicity and reactogenicity subset" in Spain ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy ***may*** ~~will~~ have ***if necessary*** one additional visit (Visit 6).

  Since the blood sampling timepoint one month post Dose 3 of the childhood vaccines does not ***always*** coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" ***may*** ~~will~~ have ***if necessary*** an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines.

Section 3

*At 7 months of age only for subjects from Spain ***(optional)***.
#At 12 months of age only for subjects from Italy ***(optional)***. At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" ***(optional)***.

Synopsis (Secondary Endpoints) and Section 10.2

- ***anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 mcg/ml***

Section 5.2

- In addition, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" (target N=300 per country) ~~will~~ ***may*** have ***if necessary*** an additional study visit because the blood sampling timepoint one month post Dose 3 of the childhood vaccines in these countries does not ***always*** coincide with study visits planned for all subjects.

Section 5.4 (Table 1)

Age Visit Timing Sampling timepoint	6-14 weeks VISIT 1 Day 0 Pre	VISIT 2 Month 1 or 2	VISIT 3 Month 3 or 4 Post vacc 2	VISIT 5	VISIT 7
Physical examination	•	•	•‡		
Recording all childhood vaccinations	•	•	•	• ***Finland/Italy only***	
Record any concomitant medication/vaccination#	•	•	•	•	•

§Additional visits ***can be*** ~~are~~ planned ***if necessary*** for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset":

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 2)

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2*	VISIT 6 ITALY only Month 9 Post-vacc 2*	 FINLAND only Month 10 Post-vacc 2*
Physical examination	•‡	•‡	•‡

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

Section 5.4 (Table 3)

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine schedule	3, 4, 5 months	3, 5, *11*-12 months	2, 3, 4 months	3, 5, 11 months	2, 4, 6 months

Section 5.5

Visit 4 is optional and may be combined with Visit 5.

Visit 6 is optional and may be combined with Visit 5.

- Physical examination. ***(Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)***

Section 5.6.2.2

In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity ***and ELISA test***, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Table 5 Laboratory Assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	***In-house***	***mcg/ml***	***0.3***

Section 5.6.4

Table 6 Serology and Stool Analysis Plan

Serology					
Post-vacc 2*	3	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP, 7 *S. pneumoniae* serotypes (France and Germany only)	Immunogenicity subset ***except Spain*** (N=15800)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), ~~serum bactericidal activity (Spain only),~~ D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	***3***	***HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)***	***N=300 from Spain***	***HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.***
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity ***and ELISA test***	N=300 from Spain	***Men C*** serum bactericidal activity ***and ELISA test***, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Section 6.1

GSK Biologicals' Infanrix Hexa®, Infanrix Polio Hib® ***and Prevenar®*** vaccines will be also supplied.

~~Prevenar® and Meningitec® if to be used during the study should be bought locally.~~

Section 6.3

All vaccines must be stored in a safe and locked place with no access for unauthorized personnel.

Vaccines will be stored at the defined range of temperature (i.e. +2 to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of temperature deviation (temperature outside the defined range, i.e. +2 to +8°C/ 36°F to 46°F) during weekends or holidays. Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

proper functioning was demonstrated during the monitor's site evaluation,

if the system continues to work in case of a power failure, and

if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working when after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag®) close to the vaccines as a back up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C/ 36°F to 46°F), must be reported within 24 hours to the Sponsor (i.e. Study Monitor/ GSK Local Contact/ GSK Biologicals)

Following exposure to a temperature deviation, vaccines will not be used until written approval is given by the sponsor.

Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.

~~All vaccines 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/ 36°F to 46°F) and must not be frozen. Storage temperature should be monitored and documented at least once per day. Monitors will check the record chart at least once per month or after any out of range storage. It is advisable to have a back-up refrigerator/ freezer in case of power failure/ breakdown. Procedures must be in place to ensure that the vaccine is kept at the indicated temperature range at all times.~~

~~The study monitor must be contacted, as soon as possible, if the cold chain is broken (e.g. vaccines become frozen or refrigeration fails).~~

~~Storage conditions for transport of vaccines from country medical department or dispatch centre to study sites or between sites are described in Appendix G.~~

Section 8.8.2

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician ~~Dr~~ [redacted] Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [redacted]

Section 10.6.2

Additional supportive and exploratory analyses will be performed (i.e. efficacy by country, efficacy against any RV GE during the second efficacy period, efficacy against severe GE, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, efficacy against hospitalization due to GE of any etiology, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system and assessment of risk factors of RV infection).

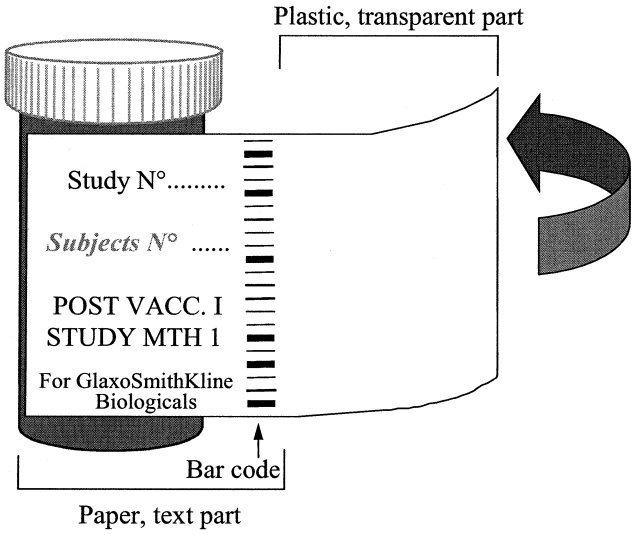
Section 10.7

In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on ~~all~~ subjects ***from the Czech Republic and Finland only*** from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data ***on solicited and unsolicited symptoms,*** immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. ***No*** study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.

Appendix C

- Recruitment was terminated on 31 January 31 2005.

Appendix D



4. Collection

Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any ~~severe~~ gastroenteritis episodes.

Appendix G

Commercially available lots will be provided for Infanrix Hexa®, Infanrix Polio Hib® and ***Prevenar®*** by GSK Biologicals, Rixensart, Belgium.

~~Prevenar® and Meningitec® vaccines will be obtained locally.~~

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site

On arrival of vaccine shipment, the ~~freeze indicator~~ ***cold chain monitoring device*** should be removed from the vaccine boxes and checked ~~after 10 minutes at room temperature~~.

Attention of ***Clinical Trials Supply Unit*** [redacted]
E-mail: [redacted]

Appendix J

Appendix J FRENCH ADMINISTRATIVE CONSIDERATIONS was added.

Attachment 1 and Attachment 2

Study contact information and sponsor updated as appropriate.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Approved by: Director, Clinical Development	[redacted] 09-06-2005 dd-mm-yyyy

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 13-JUL 2005

Study 102247 (ROTA-036)

FILE NOTE – 15 March 2006

Concerns Original Final Protocol 11 June 2004 - Co-Investigators signatures pages
Amendment 1 - 07 June 2005 Co-Investigators signatures pages
CZEC REPUBLIC

- Study Protocol finalized 11-June-2004 was signed by Prof. [redacted] (Principal Investigator) on June, 23th 2004.
- Amendment 1 issued 07-June-2005 was signed by Prof. [redacted] (Principal Investigator) on July, 13th 2005.

The Co-Investigators did not sign the Final Protocol and the Amendment 1 as Prof. [redacted] was the Co-ordinating PI.

[redacted]
(Central Study Coordinator)

Date: 15 MAR 2006.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	7 July 2005

[redacted]

NOTE TO FILE

Study: **102247 (rota-036 - Europe)**

Site #: **FINLAND** [redacted]

ITEM: **Signing of Final Protocol and Amendment #1**

Study 102247 (Rota-036 – Europe) study protocol was finalised 11-Jun-2004. Amendment #1 was issued 07-Jun-2005. At following centers in Finland there has been a change in the principal investigator (PI) between study start / final protocol (FP) and Amendment #1 (AM#1). Amendment #1 has been approved by local CA (National Agency for Medicines) on 28-Jul-2005. Following is to clarify the signing of the Protocol Investigator Agreement / Amendment approval pages at five centers:

[redacted]
- former PI [redacted] end date: 19 Apr 2005 – has signed FP
- new PI [redacted] - has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 03 Apr 2005 – has signed FP
- new PI [redacted] - has signed both FP and AM#1

[redacted]
- former PI [redacted] end date: 30 Jun 2005 – has signed FP
- new PI [redacted] - has signed AM#1

[redacted]
- former PI [redacted] end date: 30 Sep 2005 – has signed FP
- new PI [redacted] - has signed AM#1

[redacted]
- former PI [redacted] end date: 27 May 2005 – has signed FP
- new PI [redacted] - has signed FP and AM#1

Signature and date:

27 Jan 2006

[redacted]

[redacted]

Clinical Trials Manager
GlaxoSmithKline, Espoo, Finland

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	18 AUG 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	22-Aug-2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	31 AUG 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	28 Sep 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	12 SEP 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 19/Aug/2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	
Investigator signature:	[redacted]
Date:	29 Any 2005

[redacted]

CARS Id : **CLIN_200405_359**/ Version : **2.3,Admin. QC**/ Modify Date : **29/06/2005**

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	25-AUG-2005

[redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	07 Jun 2005 / 07 Oct 13 Oct 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	05 Sep 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 19 aug 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	30 AUG 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	25 AUG 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] Oct 13 Oct 2005 [redacted] 07 ~~June~~ 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	27 Sep 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 27SEP2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 13 Oct 2005 07 Oct 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	21. 11. 2005

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102247
Final

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	25.01.06

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102247
Final

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by:	
Investigator:	[redacted]
Investigator signature:	
Date:	24.1.06.

[redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with age-appropriate childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by:	
Investigator:	[redacted]
Investigator signature	
Date:	27/7/05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	14 10 05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 10/10/05

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102247
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EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	25 01 2006

CARS Id : CLIN_200405_359/ Version : 2.3,Admin. QC/ Modify Date : 29/06/2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 14/10/05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	8. 10. 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] 17 Nov 05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	_____
Date:	060106 _____

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 07.10.2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	09/12/05

[redacted]

CONFIDENTIAL 102247
Final

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 27 01 06

[redacted] [redacted] 27 Jan 06 12:34

Study 102247 (ROTA-036)

FILE NOTE – 16 March 2006

Concerns Original Protocol AM1 (07/June/04) Investigator Approval Page 9 – **France Investigator N°** [redacted] **(Dr.** [redacted]

- Quality of the copy of signature page for Principal Investigator N° [redacted] received at Rixensart at this time is poor but I hereby confirm that the Protocol Amendment 1 Summary & Approval Form has been signed by Dr. [redacted] on 26/Jan/06.

[redacted]
(Central Study Coordinator)

Date: 16/03/2006

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 26/1/06

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 08/10/2005

[redacted]

CONFIDENTIAL

102247
Final

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by:	
Investigator:	
Investigator signature:	
Date:	

[redacted]

30/11/06

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature** **Date:**	[redacted] 7-10-05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	17/10/05

Study 102247 (ROTA-036)

FILE NOTE – 15 March 2006

Concerns Original Protocol AM1 (07/June/04) Investigator Approval Page 9 – **France Investigator N°** [redacted] **(Dr.** [redacted]

- Quality of the copy of signature page for Principal Investigator N° [redacted] received at Rixensart at this time is poor but I hereby confirm that the Protocol Amendment 1 Summary & Approval Form has been signed by Dr. [redacted] on 24/Jan/06.

[redacted]
(Central Study Coordinator)

Date: 16/3/06

24/[redacted] 15:30 [redacted] [redacted]

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GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack [illegible]	[illegible]
eTrack abbreviated title	[illegible]
EudraCT number	[illegible]
Protocol title:	[illegible]
Amendment number:	Amendment 1
Amendment date:	[illegible]
Agreed by:	
Investigator:	[redacted]
Investigator's name:	[redacted]
Date:	24 Oct 06

CARS Id : CLIN_[illegible] Amendment [illegible]
S.O.Admin. [illegible] Verify Date : [illegible]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] [redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	21-10-05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	27.07.2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] 20. JULY. 2005

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	
Date:	27 Sept 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	DR. [redacted] 21. July 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature** **Date:**	[redacted] [redacted] 25.07.[redacted]5

[redacted]

[redacted]

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Dr. [redacted] **Investigator:** **Investigator signature:** **Date:**	[redacted] 25 JUL 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. med. [redacted] [redacted] 04.08.2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] [redacted] 21 JULY 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 29-7-05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	20 Jul 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Prof. [redacted] 21.8.05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signatu** **Date:**	[redacted] 20-Jun-2005

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: Dr. [redacted] **Investigator:** **Investigator signature:** **Date:** 20. Jul. 2005	

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr [redacted]
Investigator signature:	[redacted]
Date:	15.6.05

CARS Id : CLIN_200405_359/ Version : 2.3,Admin. QC/ Modify Date : 20/06/2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 20[redacted]
Agreed by: Dr. [redacted] **Investigator:** **Investigator signature:** _____ **Date:** 01-JUL-2005	

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
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EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:**	Dr. [redacted]
Investigator signature:	[redacted]
Date:	20. Juli 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 20.7.05

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr [redacted] [redacted] 20.07.01

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr [redacted] [redacted] 27 Jul 2005

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] [redacted] 21 JUL 2005

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 18 09 05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
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Amendment number:	Amendment 1
Amendment date:	07 June 2 [redacted]
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	18/07/05

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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] [redacted] 1.8.05

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EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] 10-AUG-2005

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

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EudraCT number	2004-001175-19
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Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: [redacted]	
Investigator:	
Investigator signature:	
Date:	22.5.05

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102247
eTrack abbreviated title	rota-036 - Europe
EudraCT number	2004-001175-19
Protocol title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
Amendment number:	Amendment 1
Amendment date:	07 June 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	Dr. [redacted] [redacted] 11-Aug-2005

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted] 29/07/2005

- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required document[redacted]

Investigator name:

GlaxoSmithKline File Note

INVESTIGATIONAL PRODUCT (ASSET) NAME/ NUMBER	STUDY IDENTIFIER	INVESTIGATOR NAME	CENTER NUMBER
Human Rotavirus Vaccine (444563)	102247 (ROTA-036)	Prof. [redacted]	[redacted]

Details:

This file note is intended to testify that Prof. [redacted] signed only page 4 (Investigator Agreement) for amendment n.1 of protocol Rota-036. The "Summary and Approval Page" has not been signed and will be signed secondly.

Author's Name (Print): [redacted]

Signature of Author:

Date Written: 16th March 2006

GlaxoSmithKline File Note

INVESTIGATIONAL PRODUCT (ASSET) NAME/ NUMBER	STUDY IDENTIFIER	INVESTIGATOR NAME	CENTER NUMBER
Human Rotavirus Vaccine (444563)	102247 (ROTA-036)	Prof. [redacted]	[redacted]

Details:

This file note is intended to testify that Prof. [redacted] signed only page 4 (Investigator Agreement) for amendment n.1 of protocol Rota-036. The "Summary and Approval Page" has not been signed and will be signed secondly.
Amend # 1 Investigator Agreement page 4 will be sent directly from the site to Rixensart (Attn. [redacted] by end of w/c 13th March 2006.

Author's Name (Print): [redacted]

Signature of Author:

Date Written: 16th March 2006

TITLE: ROTA-036/102247 Summary of Change Signature page Spanish PIs
DATE: 01-mar-06
BY: Monitor...
"This file note is to document that the investigators listed below who participate in study 102247/ROTA-036 in Spain were only requested to sign page 4 of the protocol Amndment 1 (07June2005) and not page 9 of the "Summary of changes of Amendment 1 section. Therefore there is no possibility to archive the original of pages 9 of the "Summary of changes of Amendment 1 for the Spanish Investigators"
Please add a table with all center number, PI last and first names, date at wich the PI signed AM1.

Center #	PI Last name	PI first name	AM1 pg 4 signed date
[redacted]	[redacted]	Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dr [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dr. [redacted]	01-Aug-2005
		Dra. [redacted]	01-Aug-2005

[redacted]

Signed by: [redacted] Date: 01-Mar-2006
Study Monitor

Study 102247 (ROTA-036)

FILE NOTE – 16 March 2006

Concerns Amendment 1 - 07 June 2005 Investigators signatures pages
SPAIN

- Approval page 4 of the Amendment 1 was signed (on 01-Aug-2005) by Dr. [redacted] (Principal Investigator-center [redacted] replacing former Principal Investigator Dr. [redacted] who retired from study Rota-036.
- Like the other Investigators of the Spanish centers for the study Rota-036, he was not requested to sign page 9 of the "Summary of changes".

[redacted]
(Central Study Coordinator)

Date: 16/03/06

NOTE TO THE FILE. Rota-036 Study (102247)

Please note that Dr. [redacted] Principal Investigator from [redacted] – centre [redacted] has been retired from the study Rota-036. This point was reported to the Spanish Minister of Health on the 29th of July 2005.

[redacted]

DATE : 29/JUL/2005

[redacted]

Clinical Reasearch Associate

Appendix 3C Sample Case Report Form

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Workbook

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Treatment number

|__|__|__|__|__|

Protocol 102247 (Rota-036)

A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

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GENERAL INSTRUCTIONS

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.

DATES

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

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 **Study Conclusion** form**.**

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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
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

One or more episodes of forceful emptying of partially digested stomach contents $\geq$ 1 hour after feeding within a day

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Diarrhea
Passage of three or more looser than normal stools (loose or watery stools), within a day

GASTROENTERITIS EPISODES

Diarrhea with or without vomiting.

INTENSITY FOR NON-SOLICITED SYMPTOMS

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: 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 attention).

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ADVERSE EVENT DEFINITIONS

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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 / Resolved

2: Recovering / Resolving: If the subject is recovering at the time the subject completes the study or at the time the subject dropped out

3: Not recovered / Not resolved: This means an AE ongoing at the time the subject completes the study or becomes lost to follow-up; if AE/SAE was ongoing at the time of death, but was not the cause of death.

4: Recovered with sequelae / Resolved with sequelae

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
prolongation of existing hospitalization
is a congenital anomaly / birth defect in the offspring of a study subject

In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours.

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GlaxoSmithKline Biologicals

102247 (Rota-036)

FLOW SHEET

Age Visit § Timing Sampling timepoint	6-14 weeks VISIT 1 Day 0 Pre	VISIT 2 Month 1 or 2	VISIT 3 Month 3 or 4 Post vacc 2	VISIT 5	VISIT 7
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in a subset: for antibody determination	● (1 ml) (N=1800)		● (3 ml) (N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations∗	●	●			
Recording all childhood vaccinations	●	●	●		
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)	●	●			
Return of reactogenicity diary cards in a subset (N=1800)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination	●	●	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●
Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

§Additional visits are planned for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset": Visit 4 will take place in Spain only and Visit 6 take place in Finland and Italy only. Visit 4 and Visit 6 are not applicable for France, Germany and the Czech Republic. Refer to Table 2 for more details.

Note: The double-line border following Month 3 indicates the interim analysis which will be performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗ The third dose of the routine childhood vaccine(s) must be given according to the respective national Immunisation plans of each country. A study visit is not planned specifically for administration of third dose of the routine childhood vaccine(s).

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

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FLOW SHEET (continued)

Age Visit Timing Sampling timepoint	VISIT 4 SPAIN only Month 5 Post-vacc 2∗	VISIT 6 ITALY only Month 9 Post-vacc 2∗	 FINLAND only Month 10 Post-vacc 2∗
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●	●	●
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in a subset: for antibody determination (3 ml)	● (target N=300 from Spain)	● (target N=300 from Italy)	● (target N=300 from Finland)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)			
Return of reactogenicity diary cards in a subset (N=1800)			
Transcription of the reactogenicity diary card in a subset (N=1800)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of routine childhood vaccinations.

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

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FLOW SHEET (continued)

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject's evaluability in the according to protocol analyses.
The local national Plan of Immunization schedules vary from country to country. The local immunization schedule should be followed to administer study vaccine concomitantly with specific childhood vaccinations at Visit 1 and Visit 2. In order to assess the safety of the study vaccine, the interval between two study vaccine doses should not be less than 30 days. Table 1 presents the interval between study visits to be followed in each specified country. Table 2 presents the age at each visit per country.

Table 1 Intervals between study visits

Interval	Czech Republic	Finland	France and Germany	Italy	Spain
Routine schedule	**3, 4, 5 months**	**3, 5, 12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccines
End of the 1st efficacy follow-up period	mid-June to end-July 2005				
one month after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable
End of the 2nd efficacy follow-up period	mid-June to end-July 2006				

Table 2 Age of the subjects at each study visits

Age at Visit	Czech Republic	Finland	France and Germany	Italy	Spain
Visit 1	3 months	3 months	2 months	3 months	2 months
Visit 2	4 months	5 months	3 months	5 months	4 months
Visit 3	6 months	6 months	5 months	6 months	6 months
Visit 4	Not applicable				7 months
Visit 5	Will vary (Visit to be completed by mid-June to end-July 2005)				
Visit 6	Not applicable	13 months	Not applicable	12 months	Not applicable
Visit 7	Will vary (Visit to be completed by mid-June to end-July 2006)				

VISIT 1

DAY 0

DOSE 1

Informed Consent has to be obtained prior to any study procedure

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Protocol
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ELIMINATION CRITERIA DURING THE STUDY

- *The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol analysis.*

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)

[C] Administration of a vaccine 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.

[D] Administration of immunoglobulins and/or any blood products during the study period.

[E] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

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CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

GSK Biologicals' HRV vaccine or placebo:
The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine 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 AE.

[F] Hypersensitivity reaction due to the vaccine.

[G] IS.

The following AEs constitute contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs 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 AE.

[H] Axillary temperature ≥ 37.5°C or rectal temperature ≥ 38.0°C..

[I] GE within 7 days preceding the study vaccine administration.

Co-administered vaccines:
For detailed information on Infanrix Hexa®, Infanrix Polio Hib®, *Neisseria meningitidis* C vaccine (e.g. Meningitec®) and *Streptococcus pneumoniae* vaccine (e.g. Prevenar®) to be co-administered with HRV vaccine or placebo, please consult the summary of product characteristics of the respective product in each country.

DTP vaccines (including Infanrix Hexa® and Infanrix Polio Hib®)
The following AEs constitute absolute contraindications to further administration of DTP vaccine; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine 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 AE:
Absolute contra-indications:

[J] Hypersensitivity reaction due to the vaccine.

[K] Encephalopathy defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours.

The following AEs constitute contraindications to administration of the study vaccine at that point in time; if any one of these AEs 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 AE.

[L] Acute disease at the time of vaccination. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e., Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).

[M] Axillary temperature ≥37.5°C (99.5°F) / Rectal temperature ≥38°C (100.4°F) / Oral temperature ≥37.5°C (99.5°F).

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CONTRAINDICATIONS TO SUBSEQUENT VACCINATION (cont)

Precautions:

[N] Fever of ≥40.5°C (rectal temperature) or ≥40.0°C (axillary temperature) within 48 hours of vaccination not due to another identifiable cause.

[O] Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.

[P] Persistent, inconsolable crying occurring within 48 hours of vaccination and lasting ! 3 hours.

[Q] Seizures with or without fever occurring within 3 days of vaccination.

Meningitec®
Absolute contraindications include:

[R] Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

[S] Acute severe febrile illness.

.

Prevenar®
Absolute contraindications include:

[T] Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

[U] Acute severe febrile illness.

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Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Center number : |__|__|__|__|__|__|

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender :
[M] ☐ Male
[F] ☐ Female

Race :
[1] ☐ Black
[4] ☐ Arabic/North African
[2] ☐ White/Caucasian
[5] ☐ East & South East Asian
[6] ☐ South Asian
[7] ☐ American Hispanic
[8] ☐ Japanese
[9] ☐ Other, please specify : _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

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102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|_____|

ELIGIBILITY CHECK

Did the subject meet all the entry criteria ?

☐ Yes ☐ No → If No, tick (✓) all boxes corresponding to violations of any inclusion/exclusion criteria.

Do not enter the subject into the study if he/she failed any inclusion or exclusion criteria below.

INCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the inclusion criteria the subject failed

[1] ☐ Subjects who the investigator believes that their parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits, collection of stool samples) should be enrolled in the study.

[2] ☐ A male or female between, and including, 6 and 14 weeks (42 – 104 days) of age at the time of the first vaccination.

[3] ☐ Written informed consent obtained from the parent or guardian of the subject.

[4] ☐ Free of obvious health problems as established by medical history and clinical examination before entering into the study.

[5] ☐ Birth weight > 2000g.

EXCLUSION CRITERIA

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.

[8] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)

[9] ☐ History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B disease (in all subjects). Only for subjects in Spain: history of meningococcal group C disease. Only for subjects in France and Germany: history of disease caused by *Streptococcus pneumoniae*.

[10] ☐ History of use of experimental rotavirus vaccine.

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Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|_____|

ELIGIBILITY CHECK

EXCLUSION CRITERIA (continued)

[11] ☐ Previous vaccination against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (in all subjects). Only for subjects in Spain: previous vaccination against meningococcal group C. Only for subjects in France and Germany: previous vaccination against *Streptococcus pneumoniae*.

[12] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract, IS or other medical condition determined to be serious by the investigator.

[13] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

[14] ☐ History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

[15] ☐ Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).)

[16] ☐ Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).

[17] ☐ A family history of congenital or hereditary immunodeficiency.

[18] ☐ Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.

[19] ☐ History of any neurologic disorders or seizures.

[20] ☐ Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number |__|__|__|__|__|

3.

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Protocol	CRF	Visit		Subject Number
102247	|___|	**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 tick (✓) appropriate box(es) and give diagnosis.

	DIAGNOSIS		PAST	CURRENT
[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]	**Muskuloskeletal**	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.

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Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|_____|

LABORATORY TESTS

BLOOD SAMPLE (in a subset for Finland)

Has a blood sample been taken ?

☐ Yes " Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

☐ NA

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

EPIDEMIOLOGICAL DATA

Number of siblings : |_____|

Attendance to day care center : ☐ Yes
☐ No

5.

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Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|__|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|**.** |__|°C → Route : [A] ☐ Axillary
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or Placebo** [R] ☐ Replacement vial → |__|__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

Comments : _____

(*) Why not administered ?

Please tick the **ONE most appropriate** category for non administration :

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N° : |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N°: |__|__| or Solicited AE code : |__|__|

☐ [OTH] Other, please specify : _____
(e.g. : consent withdrawal, protocol violation, …)

Please tick who took the decision : [I] ☐ Investigator [P] ☐ Parents/Guardians

If regurgitation or vomiting occurs after vaccination, no additional HRV vaccine/placebo dose should be administered at this visit.

IMMEDIATE POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time (30 minutes) please fill in the **Solicited Adverse Events** section**,** the **Non-Serious Adverse Event** section or a **Serious Adverse Event** form**.**

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box**.**

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Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 1**		|_____|

CONCOMITANT VACCINE ADMINISTRATION

Infanrix hexa

☐ No
☐ Yes → please complete the date : |__|__| |___|___| |____|____|
day month year

Meningitec (Spain only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |___|___| |____|____|
day month year
☐ NA

Prevenar (France & Germany only, NA for the other countries)

☐ No
☐ Yes → please complete the date : |__|__| |___|___| |____|____|
day month year
☐ NA

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

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Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 1**		|_____|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

Has the subject experienced any of the following signs/symptoms including diarrhea during the solicited period?

[91] ☐ Information not available
[92] ☐ No vaccine administered
[0] ☐ No
[1] ☐ Yes, please **tick** No/Yes **for each symptom.** If Yes is ticked, please **complete** all items.

GENERAL SYMPTOMS	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Ongoing after day 7?**	**Date of last day of symptoms day month year**	**Causality?**	Medical attention
Fever (FE) ☐ No ☐ Yes → °C : [A] ☐ Axillary [R] ☐ Rectal	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Cough / Runny nose (CO) ☐ No ☐ Yes → intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Irritability/ Fussiness (IR) ☐ No ☐ Yes → intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Loss of appetite (LO) ☐ No ☐ Yes → intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Vomiting (VO) ☐ No ☐ Yes → number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|

Intensity:
0
1
2
3

Fever: Axillary ! 37.5°C
Rectal ! 38°C

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

If any of these **adverse events** are **serious** according to Protocol definition, please report event to GSK monitor by telephone or fax within 24 hours (see Protocol) and complete the **Serious Adverse Event form**.

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102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 1**		|_____|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?	Causality?	Medical attention
Diarrhea (DA)(*) ☐ No ☐ Yes (**) → number of looser than normal stools:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→ please fill the GE section	☐ No ☐ Yes	☐ No ☐ Yes→ HO/ER/MD/AD |___|

(*) Stool sample should be collected in case of diarrhea.

Stool collection date : |___| |___| |____| Hour : |___| |___|
day month year hours min

Stool collection date : |___| |___| |____| Hour : |___| |___|
day month year hours min

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

(**) If diarrhea yes, please complete the following items.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Irritability/less playfull	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for diarrhea :

☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

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Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|_____|

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination ?

[91] ☐ Information not available

[92] ☐ No Vaccine administered

[0] ☐ No

[1] ☐ Yes, fill in the Non-Serious Adverse Event pages or Serious Adverse Event form.

10.

VISIT 2

MONTH 1 or 2

Dose 2

30 – 48 days after Visit 1 for Czech Republic, France and Germany

49 – 83 days after Visit 1 for Finland, Italy and Spain

CONFIDENTIAL

REMINDERS

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.

ADVERSE EVENTS

Please report adverse events as specified in the Protocol and fill in the **Non-Serious Adverse Events** pages or the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa, Infanrix PolioHib, Prevenar and Meningitec in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 2**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 2 ?

☐ Yes, please complete the next pages.
☐ No

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: |___|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |___| or solicited AE code : |___|

☐ [OTH] Other, please specify : _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision : [I] ☐ Investigator [P] ☐ Parents/Guardians

11.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 2**	|___|_____|_____| day month year	|_____|

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from one week after dose 1 until visit 2?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes
☐ No

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|____|	**VISIT 2**		|__|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|**.** |__|°C → Route : [A] ☐ Axillary
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or Placebo** [R] ☐ Replacement vial → |__|__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

Comments : _____

(*) Why not administered ?

Please tick the **ONE most appropriate** category for non administration :

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N° : |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N°: |__|__| or Solicited AE code : |__|__|

☐ [OTH] Other, please specify : _____
(e.g. : consent withdrawal, protocol violation, …)

Please tick who took the decision : [I] ☐ Investigator [P] ☐ Parents/Guardians

If regurgitation or vomiting occurs after vaccination, no additional HRV vaccine/placebo dose should be administered at this visit.

IMMEDIATE POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time (30 minutes) please fill in the **Solicited Adverse Events** section**,** the **Non-Serious Adverse Event** section or a **Serious Adverse Event** form**.**

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box**.**

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 2**		|_____|

CONCOMITANT VACCINE ADMINISTRATION

Infanrix hexa (NA for France)

- ☐ No
- ☐ Yes → please complete the date : \|__\|__\| \|___\|___\| \|_____\| (day / month / year)
- ☐ NA

Infanrix polio Hib (France only, NA for the other countries)

- ☐ No
- ☐ Yes → please complete the date : \|__\|__\| \|___\|___\| \|_____\| (day / month / year)
- ☐ NA

Meningitec (Spain only, NA for the other countries)

- ☐ No
- ☐ Yes → please complete the date : \|__\|__\| \|___\|___\| \|_____\| (day / month / year)
- ☐ NA

Prevenar (France & Germany only, NA for the other countries)

- ☐ No
- ☐ Yes → please complete the date : \|__\|__\| \|___\|___\| \|_____\| (day / month / year)
- ☐ NA

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 2**		|_____|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

Has the subject experienced any of the following signs/symptoms including diarrhea during the solicited period?

[91] ☐ Information not available
[92] ☐ No vaccine administered
[0] ☐ No
[1] ☐ Yes, please **tick** No/Yes **for each symptom.** If Yes is ticked, please **complete** all items.

GENERAL SYMPTOMS	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Ongoing after day 7?**	**Date of last day of symptoms day month year**	**Causality?**	Medical attention
Fever (FE) ☐ No ☐ Yes → °C : [A] ☐ Axillary [R] ☐ Rectal	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	—.— ☐ not taken	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Cough / Runny nose (CO) ☐ No ☐ Yes → intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Irritability/ Fussiness (IR) ☐ No ☐ Yes → intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Loss of appetite (LO) ☐ No ☐ Yes → intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|
Vomiting (VO) ☐ No ☐ Yes → number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|___|____|	☐ No ☐ Yes	HO/ER/MD/AD ☐ No ☐ Yes→ |__|

Intensity:
0
1
2
3

Fever: Axillary ! 37.5°C
Rectal ! 38°C

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

If any of these **adverse events** are **serious** according to Protocol definition, please report event to GSK monitor by telephone or fax within 24 hours (see Protocol) and complete the **Serious Adverse Event form**.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**DOSE 2**		|__|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS (in a subset for Finland)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?	Causa-lity?	Medical attention
Diarrhea (DA)(*) ☐ No ☐ Yes (**) → number of looser than normal stools:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→ please fill the GE section	☐ No ☐ Yes	☐ No ☐ Yes→ HO/ER/MD/AD |__|__|

(*) Stool sample should be collected in case of diarrhea.

Stool collection date : |__|__| |__|__|__| |__|__|__|__| Hour : |__|__| |__|__|
day month year hours min

Stool collection date : |__|__| |__|__|__| |__|__|__|__| Hour : |__|__| |__|__|
day month year hours min

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

(**) If diarrhea yes, please complete the following items.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Irritability/less playfull	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for diarrhea :

☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 2**		|_____|

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination ?

[91] ☐ Information not available

[92] ☐ No Vaccine administered

[0] ☐ No

[1] ☐ Yes, fill in the Non-Serious Adverse Event pages or Serious Adverse Event form.

17.

VISIT 3

MONTH 3 or 4

30 – 48 days after Visit 2 for Finland and Italy

49 – 83 days after Visit 2 for Czech Republic, France, Germany and Spain

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa, Infanrix PolioHib, Prevenar and Meningitec in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 3**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 3 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

18.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|___|	**VISIT 3**	|__|__| |___|___| |___|___|___| day month year	|___|___|___|___|___|___|

LABORATORY TESTS

BLOOD SAMPLE (in a subset for Finland)

Has a blood sample been taken ?

☐ Yes " Please complete only if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

☐ No

☐ NA

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from one week after dose 2 until visit 3 ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

CONCOMITANT VACCINE ADMINISTRATION

According to the local national Plan of Immunization, the third dose of routine vaccinations should be done at 4 months age in France and Germany at 5 months age in Czech republic and at 6 months age in Spain.
Please report the vaccine administration date :

Infanrix hexa (France, Germany, Spain and Czech Republic only, NA for the other countries)

☐ No

☐ Yes → please complete the date : \|__\|__\| \|___\|___\|___\| day month year

☐ NA

Prevenar (France & Germany only, NA for the other countries)

☐ No

☐ Yes → please complete the date : \|__\|__\| \|___\|___\|___\| day month year

☐ NA

Meningitec (Spain only, NA for the other countries)

☐ No

☐ Yes → please complete the date : \|__\|__\| \|___\|___\|___\| day month year

☐ NA

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

19.

CONFIDENTIAL

VISIT 4

MONTH 5

30 – 48 days after the third dose of childhod vaccines

SPAIN ONLY

CONFIDENTIAL

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa, Infanrix PolioHib, Prevenar and Meningitec in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 4**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 4 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|____|	**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes " Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 3 until visit 4 ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

VISIT 5

mid June to end July 2005

End of the first efficacy follow-up period

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events.

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.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 5**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 5 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: \|__\|__\|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : \|__\|__\| or solicited AE code : \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

22.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|___|	**VISIT 5**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 3 until visit 5 (from Visit 4 to Visit 5 in Spain)?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

23.

CONFIDENTIAL

GASTROENTERITIS EPISODES UP TO VISIT 5

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

Has any gastroenteritis occurred from Visit 1 until Visit 5 excluding those recorded on the solicited adverse event pages or has any gastroenteritis occurred during the solicited period and was still ongoing after day 7 ?

☐ No
☐ Yes " Please complete below and next pages if necessary.

> ***One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.***
> ***A second stool sample can be taken if the first one is insufficient.***

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Medical attention:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

***Date** The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)
|__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Medical attention:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ___________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

|__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

<u>Medical attention</u>:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

|__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

<u>Medical attention</u>:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE UP TO VISIT 5

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes :
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

__Medical attention__:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel (Visit)
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

CONFIDENTIAL

CONCOMITANT

VACCINATION

UP TO VISIT 5

CONFIDENTIAL

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|__|

CONCOMITANT VACCINATION UP TO VISIT 5

Has any vaccine other than the study vaccine(s) and the routine vaccine been administered during the timeframe as specified in the Protocol up to Visit 5 ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** day month year
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IV = Intravenous
NA = Intranasal
OTH = Other
PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

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CONFIDENTIAL

MEDICATION
UP TO VISIT 5

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GlaxoSmithKline Biologicals

Medication route. Please use below defined codes.

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

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study vaccine (HRV vaccine or placebo) are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever is later) are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for adverse events must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment.

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102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

MEDICATION UP TO VISIT 5

Have any medications/treatments been administered during the timeframe as specified in the protocol up to Visit 5 ?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick 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					

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CONFIDENTIAL

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 5

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 5

(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 between Visit 1 and Visit 5 or has any non-serious adverse events leading to drop-out occurred ?

☐ No
☐ Yes, please complete the following table.

AE No.	1	2
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

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102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|			|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 5 (continued)

AE No.	3	4
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

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STUDY

CONCLUSION

AT VISIT 5

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|_____|

STUDY CONCLUSION AT VISIT 5

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 1 and Visit 5 ?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 1 and Visit 5 ?

☐ No ☐ Yes → Complete date and tick one reason below.

|__|__| |__|__|__| |__|__|__|__|
day month year

[1] ☐ Medical emergency requiring identification of investigational product for further treatments

[9] ☐ Other, specify: _____

→ Complete **Non-Serious Adverse Event** section or **Serious Adverse Event** form as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 1 and Visit 5 ?

☐ No ☐ Yes → Specify: _____

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102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

STUDY CONCLUSION AT VISIT 5 (continued)

Was the subject withdrawn from study?

☐ No
☐ Yes

Please tick the **ONE most appropriate** category for withdrawal.

☐ [SAE] Serious adverse event
(check **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event
(check the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [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: _____

Please tick who took decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

34.

VISIT 6

MONTH 9 (Italy)
MONTH 10 (Finland)

30 – 48 days after the third dose of childhod vaccines

ITALY AND IMMUNO SUBSET FOR FINLAND ONLY

CONFIDENTIAL

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination other than Infanrix Hexa in the **Concomitant Vaccination** section.

PHYSICAL EXAMINATION

Please perform a physical examination

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 6**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 6 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|___|	**VISIT 6**	|__|__| |___|___| |___|___|___| day month year	|___|___|___|___|___|___|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes " Please complete only if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

☐ No

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 5 until visit 6 ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

CONCOMITANT VACCINE ADMINISTRATION

According to the local national Plan of Immunization, the third dose of routine vaccinations should be done at 11months age in Italy and 12 months age in Finland.
Please report the vaccine administration date :

Infanrix hexa

☐ No

☐ Yes → please complete the date : \|__\|__\| \|___\|___\| \|___\|___\|___\| day month year

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

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VISIT 7

mid June to end July 2006

End of the second efficacy follow-up period

REMINDERS

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report any non-serious adverse event leading to drop-out and fill in the non-serious adverse events pages. Please report serious adverse events as specified in the Protocol and fill in the **Serious Event (SAE)** form, as appropriate. This SAE form must be faxed to GlaxoSmithKline within 24 hours of you becoming aware of these events

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 7**		|_____|

CHECK FOR STUDY CONTINUATION

Did the subject come at visit 7 ?

☐ Yes → please complete the following pages.

☐ No → please complete below :

☐ Same reason and decision as previous visit.

OR

Please tick the **ONE most appropriate** reason and skip the following pages of this visit.

☐ [SAE] Serious adverse event (complete the **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event (complete the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

Please tick who took the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit	Date of visit	Subject Number
102247	|___|	**VISIT 7**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present diarrhea during the period starting from visit 5 until visit 7 (from Visit 6 until Visit 7 in Finland and Italy) ?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis section**

→ please collect a stool sample as soon as possible after diarrhea begins and not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis** section.

EPIDEMIOLOGICAL DATA

Attendance to day care center : ☐ Yes ☐ No

CONFIDENTIAL

GASTROENTERITIS EPISODES

VISIT 5 TO 7

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Has any gastroenteritis occurred from Visit 5 until Visit 7 ? ☐ No
☐ Yes " Please complete below and next pages if necessary.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

<u>Medical attention</u>:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date ***The first and last date to be considered is the first and last date with at least 3 looser than normal stools.*** day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

GlaxoSmithKline

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

<u>Medical attention</u>:

HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date ***The first and last date to be considered is the first and last date with at least 3 looser than normal stools.*** day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

|__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

<u>Medical attention</u>:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

<u>Medical attention</u>:

HO:	Hospitalization
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MD:	Medical Personnel (Visit)
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(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Episode n° |__|__|

Treatment: ☐ No
☐ Yes " If yes : ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical attention : ☐ No
☐ Yes " |__|__| HO/ER/MD/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

|__|__| |__|__|__| |__|__|__|__| (day month year) |__|__|:|__|__| (hours min)

One single stool sample should be collected as soon as possible <u>and</u> not later than 7 days after the beginning of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

<u>Medical attention</u>:

HO:	Hospitalization
ER:	Emergency Room
MD:	Medical Personnel
AD:	Medical contact without visit

(Refer to protocol for full definition)

Date *The first and last date to be considered is the first and last date with at least 3 looser than normal stools.* day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature** °C	" ☐ Axillary ☐ Rectal	**Irritability / Less playfull**	**Lethargic**	**Listless**	**Seizure**
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

CONCOMITANT

VACCINATION

VISIT 5 TO 7

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) and the routine vaccine been administered during the timeframe as specified in the Protocol between Visit 5 and Visit 7 ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	**Route**	**Administration date** day month year
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		
		|__|__| |__|__|__| |__|__|__|__|
For GSK		

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IV = Intravenous
NA = Intranasal
OTH = Other
PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

44.

CONFIDENTIAL

MEDICATION
VISIT 5 TO 7

CONFIDENTIAL

GlaxoSmithKline Biologicals

Medication route. Please use below defined codes.

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

All concomitant medication, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study vaccine and ending one month (minimum 30 days) after the last dose of the study vaccine (HRV vaccine or placebo) are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or the last dose of the routine primary vaccination course (whichever is later) are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

Concomitant medication administered for the treatment of an AE or SAE within the follow-up period for adverse events must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment.

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102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments been administered between Visit 5 and Visit 7 ?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	**Medical Indication**	**Total daily dose**	**Route**	**Start and end date or tick 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					

CONFIDENTIAL

NON-SERIOUS ADVERSE EVENTS VISIT 5 TO 7

To be filled only in case of drop-out due to non-serious AE.

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF	Visit		Subject Number
102247	|___|	**VISIT 1**		|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP-OUT

AE No.	1	2
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF				Subject Number
102247	|___|			|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP OUT (continued)

AE No.	3	4
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (protocol specific: 15 minutes – 30 minutes)
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medical attention (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalization ER: Emergency Room MD: Medical Personnel (Visit) AD: Medical contact without visit	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

STUDY

CONCLUSION

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|_____|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 5 and Visit 7 ?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 5 and Visit 7 ?

☐ No ☐ Yes → Complete date and tick one reason below.

|__|__| |__|__|__| |__|__|__|__|
day month year

[1] ☐ Medical emergency requiring identification of investigational product for further treatments

[9] ☐ Other, specify: _____

→ Complete **Non-Serious Adverse Event** section or **Serious Adverse Event** form as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 5 and Visit 7 ?

☐ No ☐ Yes → Specify: _____

CONFIDENTIAL

102247 (Rota-036)

Protocol	CRF			Subject Number
102247	|___|			|__|__|__|__|__|__|

STUDY CONCLUSION (continued)

Was the subject withdrawn from study?

☐ No
☐ Yes

Please tick the **ONE most appropriate** category for withdrawal.

☐ [SAE] Serious adverse event
(check **Serious Adverse Event** form)

Please specify SAE N°: |__|__|

☐ [AEX] Non-Serious adverse event
(check the **Non-serious Adverse Event** section)

Please specify unsolicited AE N° : |__|__| or solicited AE code : |__|__|

☐ [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: _____

Please tick who took decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 1	|__|__|__|__|__|__|__|

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting,

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

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms (day month year)	Medical attention	HO/ER/MD/AD
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__||__|__|__|__|	☐ No ☐ Yes →	|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__||__|__|__|__|	☐ No ☐ Yes →	|__|__|
Irritability/ Fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__||__|__|__|__|	☐ No ☐ Yes →	|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__||__|__|__|__|	☐ No ☐ Yes →	|__|__|
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__||__|__|__|__|	☐ No ☐ Yes →	|__|__|

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 1	|__|__|__|__|__|__|__|

SOLICITED GENERAL SYMPTOMS

II. Diarrhea

DIARRHEA is defined as three or more looser than normal stools within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	
Diarrhea (*) →number of looser than normal stools :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	If ongoing after day 7, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET

(*) In case of diarrhea (three or more looser than normal stools within a day) please collect a stool sample, assess the occurrence of any of the following symptoms, record whether medical treatment was given and if medical advise has been taken.

DIARRHEA	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Stools samples taken. ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION

- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 1	|__|__|__|__|__|__|__|

FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM

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.

In case of diarrhea starting between day 0 and day 7 and still ongoing on day 7, please continue to assess the following symptoms until the end of the diarrhea.

DIARRHEA	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea → number of looser than normal stools :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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 HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**DOSE 1**	

UNSOLICITED SYMPTOMS

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:	**Mild:**	An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2:	**Moderate:**	An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3:	**Severe:**	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).

GENERAL SYMPTOMS OTHER THAN DIARRHEA OR OTHER SOLICITED SYMPTOMS

Description - please give details below	Intensity	Start date day month year	End date or check box if continuing day month year		Medical attention	
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD

Medical attention:

HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

MEDICATION

Please fill in below if any medication has been taken since the vaccination

Trade/Generic name	Reason	Route	Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
						☐
						☐
						☐
						☐
						☐
						☐
						☐

Protocol		**DIARY CARD**		Subject number
102247 (Rota-036)			**From day 8 after dose 1 until dose 2**	_____

GASTROENTERITIS EPISODE

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 with or without vomiting.

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, record whether medical treatment was given and if medical advise has been taken.

EPISODE N° : _____

GASTROENTERITIS SYMPTOMS	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
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION

- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __/__/____

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 2	|__|__|__|__|__|__|__|

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting,

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

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms (day month year)	Medical attention	HO/ER/MD/AD
Temperature → °C: ☐ Axillary ☐ Rectal	—.—	—.—	—.—	—.—	—.—	—.—	—.—	—.—	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|	☐ No ☐ Yes →	|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|	☐ No ☐ Yes →	|__|__|
Irritability/ Fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|	☐ No ☐ Yes →	|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|	☐ No ☐ Yes →	|__|__|
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|	☐ No ☐ Yes →	|__|__|

Medical attention:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__\|__||__\|__\|__||__\|__\|__\|__\|

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**DOSE 2**	|__|__|__|__|__|__|__|

SOLICITED GENERAL SYMPTOMS

II. Diarrhea

DIARRHEA is defined as three or more looser than normal stools within a day.

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	
Diarrhea (*) →number of looser than normal stools :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	If ongoing after day 7, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET

(*) In case of diarrhea (three or more looser than normal stools within a day) please collect a stool sample, assess the occurrence of any of the following symptoms, record whether medical treatment was given and if medical advise has been taken.

DIARRHEA	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Stools samples taken. ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION

- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			DOSE 2	_____

FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM

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.

In case of diarrhea starting between day 0 and day 7 and still ongoing on day 7, please continue to assess the following symptoms until the end of the diarrhea.

DIARRHEA	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20
Temperature → °C: ☐ Axillary ☐ Rectal	__._	__._	__._	__._	__._	__._	__._	__._	__._	__._	__._	__._	__._
Vomiting → number:	__	__	__	__	__	__	__	__	__	__	__	__	__
Diarrhea → number of looser than normal stools :	__	__	__	__	__	__	__	__	__	__	__	__	__
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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 HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**DOSE 2**	

UNSOLICITED SYMPTOMS

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: **Mild:** An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2: **Moderate:** An adverse event which is sufficiently discomforting to interfere with normal everyday activities.

3: **Severe:** 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).

GENERAL SYMPTOMS OTHER THAN DIARRHEA OR OTHER SOLICITED SYMPTOMS

Description - please give details below	Intensity	Start date day month year	End date or check box if continuing day month year		Medical attention	
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD
				☐	☐ No ☐ Yes →	HO/ER/MD/AD

Medical attention:

HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel (Visit)
AD: Medical contact without visit
(Refer to protocol for full definition)

MEDICATION	Please fill in below if any medication has been taken since the vaccination					
Trade/Generic name	Reason	Route	Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
						☐
						☐
						☐
						☐
						☐
						☐
						☐

Protocol		DIARY CARD		Subject number
102247 (Rota-036)			**From Day 8 after Dose 2 until Study End**	_____

GASTROENTERITIS EPISODE

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 with or without vomiting.

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, record whether medical treatment was given and if medical advise has been taken.

EPISODE N° : _____

GASTROENTERITIS SYMPTOMS	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
Irritability / Less playful?	☐ 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
Lethargic?	☐ 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
Listless?	☐ 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
Seizure?	☐ 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:
- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify : _____

MEDICAL ATTENTION
- ☐ Hospitalisation
- ☐ Emergency room
- ☐ Medical Personnel (Visit)
- ☐ Medical contact without visit
- ☐ None

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON __/__/____

IN CASE OF HOSPITALISATION, PLEASE INFORM ..... ☎: .....

Appendix 3D List of Independent Ethics Committees/Institutional Review Boards

Centre Numbers*	Ethics Review Body	Location
CZECH REPUBLIC		
All centers		
FINLAND		
All centers		

Centre Numbers*	Ethics Review Body	Location
FRANCE		
All centers	[redacted]	[redacted]
GERMANY		
All centers	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany

Centre Numbers*	Ethics Review Body	Location
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
[redacted]	[redacted]	[redacted] Germany
ITALY		
[redacted]	[redacted]	[redacted] (Italy)
[redacted]	[redacted]	[redacted] (Italy)
SPAIN		
All centers	[redacted]	[redacted]

*GSK Biologicals assigned centre number [redacted] (Italy) was the original ERC for this center and was replaced by the ERC stated in the table during the course of the study.

Appendix 3E Representative written information for patient and sample consent forms

GlaxoSmithKline Biologicals

Rue de l'Institut 89

1330 Rixensart, Belgium

Confidential & Proprietary Information

Subject Information Sheet and Informed Consent Agreement

GLAXOSMITHKLINE BIOLOGICALS

Subject/Patient Information Sheet and Informed Consent

Study title: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Investigator:

Sponsor: GlaxoSmithKline Biologicals

eTrack study number: 102247

eTrack abbreviated title: rota-036 - Europe

EudraCT number 2004-001175-19

Date of approval: 11 June 2004 – Final Version 1

07 June 2005 –Version 2 (amendment 1)

Prepared by: [redacted] Scientific Writer

CLINICAL RESEARCH AND DEVELOPMENT

GlaxoSmithKline Biologicals

This document should be presented to the subject or patient in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Subject Information Sheet & Informed Consent

etrack Protocol No. 102247 (rota-036)

Subject No._____ Date: _____

Introduction

The main objective of this document is to provide the potential study participant with the information necessary to help in deciding to participate in the study with GlaxoSmithKline Biologicals' human rotavirus (HRV) vaccine. The document provides a full but simple understanding of the scientific reasons for investigation of the vaccine, the characteristics, effectiveness and safety of the vaccine, the likely effects and benefits of the study vaccine in the subjects. This document also informs subjects about their rights and responsibilities in participating in the trial.

Rotavirus Disease

The most common cause of diarrheal illness in infants and young children is a virus called "rotavirus". Virtually all children suffer from rotavirus diarrhea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhea with or without vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrheal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Indeed, gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is a leading cause of death in poorer countries.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. GSK Biologicals has developed a new rotavirus vaccine (HRV vaccine) based on a **human rotavirus**. The human rotavirus in the new vaccine has been weakened so that when a child swallows the vaccine, it causes only a mild infection with few or no symptoms. The child is expected to develop antibodies (substance in the blood that fights infection) and thus be protected against rotavirus gastroenteritis.

As of 31 March 2004, over 74,450 infants have been enrolled in clinical trials with GSK Biologicals' HRV vaccine. The HRV vaccine was shown to be safe and well tolerated in adults, children (1-3 years old) and infants (approximately 2 months old). The mild side-effects observed in infants vaccinated with the HRV vaccine were similar to those observed in infants who were given a placebo (a product that looks like the vaccine but has no activity). Also refer to section "Risks associated with the study" on page 9.

GSK Biologicals HRV vaccine was also effective in developing specific antibodies in infants and decreased the occurrence of acute and severe rotavirus gastroenteritis during two years after vaccination in Finland and Latin America (Brazil, Mexico and Venezuela). The HRV vaccine also reduces hospitalization due to rotavirus disease.

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etrack Protocol No. 102247 (rota-036)

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The purpose of the study

This study will be conducted in several countries in the European Union.

The main purpose of this study is to test the efficacy (prevent acute rotavirus gastroenteritis), safety, reactogenicity (side-effects) and immunogenicity (ability to develop antibodies to fight infection) of GSK Biologicals' HRV vaccine in infants when given along with specific childhood vaccinations used in Europe.

A total of 3990 infants will be part of this study (target of 300 infants each in Czech Republic, France, Germany, Italy and Spain and target of 2490 in Finland). Depending on the current practice for routine vaccinations for children, your child/ward will receive the HRV vaccine or placebo twice by mouth, 1 or 2 months apart. Your child's/ward's participation in this study will last until mid-June to end-July 2006.

Some infants will get a placebo (looks like vaccine but has no activity) instead of the HRV vaccine in order to see if any side effects that occur are related to the rotavirus vaccine. Neither you nor your doctor will know whether your child/ward got the HRV vaccine or the placebo until the end of the study (blinded). If needed in case of emergencies, however, the doctor will be given this information.

Approval

This study protocol has been reviewed and accepted by an independent ethics review committee/Institutional review board.

Study Participation

The research staff member will ask you questions to determine if your child/ward can participate in this study.

Once it is determined that your child/ward can participate in the study, you will be asked to read and sign an informed consent. If you give consent for your child/ward to join the study, the doctor will give your child/ward a physical examination. A research staff member will ask you questions about your family composition, your child's/ward's medical history and the medicines that your child/ward may be taking. At each visit, you will also be asked if your child frequents a day care center or not.

Your child/ward will be randomly assigned (like flipping a coin) to one of two groups, with a 2 out of 3 chance of receiving the HRV vaccine and a 1 out of three chance of receiving a placebo. Each child will receive two doses given one or two months apart by mouth. All study subjects will be observed closely for at least 30 minutes following the administration of vaccines.

Subject Information Sheet & Informed Consent

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Following the national Plan of Immunisation schedule in your country, your child/ward will also receive the following routine childhood vaccinations:

Country	**Vaccinations**	
	Visit 1	**Visit 2**
Czech Republic	Infanrix Hexa®	Infanrix Hexa®
Finland	Infanrix Hexa®	Infanrix Hexa®
France	Infanrix Hexa® and Prevenar®	Infanrix Polio Hib ® and Prevenar®
Germany	Infanrix Hexa® and Prevenar®	Infanrix Hexa® and Prevenar®
Italy	Infanrix Hexa®	Infanrix Hexa®
Spain	Infanrix Hexa® and Meningitec®	Infanrix Hexa® and Meningitec®

Infanrix Hexa®: combination vaccine providing immunization against diphtheria, tetanus, pertussis, Hib, Hepatitis B and poliovirus.
Infanrix Polio Hib®: combination vaccine providing immunization against diphtheria, tetanus, pertussis, Hib and poliovirus
Prevenar®: immunization against Pneumococcal disease.
Meningitec®: immunization against Neisseria meningitidis. Note: Other similar licensed vaccines against MenC may be substituted if Meningitec® is not available.

Thereafter, your child/ward will complete his/her routine childhood vaccination course as per the recommended local national Plan of Immunisation schedule.

The childhood vaccines in this study are licensed for routine infant vaccination course in many countries worldwide and specifically also in the countries where they will be used. Infanrix Hexa® and Prevenar® are licensed in all countries of the European Union, Infanrix Polio Hib® is licensed in France and Meningitec® is licensed in Spain.

All children in this study will have five study visits. If you live in Spain, your child/ward may have an additional study visit at 7 months of age ***if necessary***. If you live in Italy, your child/ward may have an additional study visit at 12 months of age ***if necessary***. If you live in Finland, your child/ward may have an additional study visit at 13 months of age ***if necessary***. The research staff member will notify you if your child/ward will need an additional study visit. (**Amendment 1: 07 June 2005)**

During the study, you should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

Your child/ward will be followed for diarrhea starting from the time of the first vaccine dose until your child completes the study. You will be regularly contacted during the study period to check on your child's/ward's health – if he/she has any diarrhea or any serious illness. During each rotavirus season (from December to end of May), you will be contacted approximately weekly to check if your child/ward had any diarrhea or serious illness. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. Out of the rotavirus season (June to November) you will be contacted approximately every two weeks. In case you are unavailable at the time of contact, at least one more attempt will be made to contact you before the next planned contact.

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If your child/ward develops gastroenteritis (diarrhea with or without vomiting) at any time during the study, you will be asked to complete a "GE" diary card until end of that diarrhea episode. Diarrhea is defined as passage of 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. You will be also asked to provide a stool sample from your child/ward whenever you child/ward develops gastroenteritis and return the samples to the investigator on an ongoing basis. The stool sample should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of gastroenteritis symptoms. Samples collected during the study will be analysed by GSK Biologicals' designated laboratory to detect rotavirus. We will evaluate the number of rotavirus gastroenteritis cases in the group of infants that got the HRV vaccine compared to the group that got placebo to assess the effectiveness of the HRV vaccine. The GE card has short questions on how long and severely sick your child has been, and what medical care you sought, if any.

You may be asked to complete a "Reactogenicity" diary card daily during the first eight days after each HRV vaccine or placebo dose and other vaccines. You will then fill out information on any diarrhea, vomiting, fever, irritability/fussiness, loss of appetite or cough/runny nose during the first eight days after each HRV vaccine or placebo dose. The information collected will allow us to evaluate how your baby feels after vaccination. This information will be collected from 300 children in each country.

You will also receive a "unsolicited AE/medication" diary card to record information on any adverse events that occur between Visit 1 and Visit 3 and to record any medication taken by your child/ward during that time.

Two (in Czech Republic, France and Germany) or three (in Finland, Italy and Spain) blood samples will be taken from 300 children in each country. A blood sample (approximately 1 ml or 1/4 teaspoon) may be taken from your child/ward at Visit 1. A second blood sample (approximately 3 ml or 3/4 teaspoon) may be taken at Visit 3. Children in Spain, Italy and Finland ***will have an additional blood sample (approximately 3 ml or 3/4 teaspoon)*** one month after the third dose of the routine vaccination course. Blood samples collected during the study will be analysed by GSK Biologicals' designated laboratory to detect antibodies to HRV vaccine and other childhood vaccines. (**Amendment 1: 07 June 2005)**

The research staff will review all the study procedures with you in detail. A brief description of the study procedures during each study visit is presented below.

In between these visits you will be asked to provide in all cases of diarrhea a stool sample from your child/ward as early as possible and within 7 days of the diarrhea episode, and complete a GE card.

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Visit 1 (6 to 14 weeks of age):

- You will be asked questions about your child's/ward's health, your child/ward will be examined by the doctor
- You might be asked for a blood sample (1 ml or 1/4 teaspoon) from your child/ward.
- Administration of the first dose of the study vaccines (HRV vaccine or placebo).
- Administration of the first dose of the specific childhood vaccines.
- After vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- You might be asked to complete the "Reactogenicity" diary card.
- You should complete the "unsolicited AE/medication" diary card.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.

Visit 2 (30-48 days after Visit 1 in the Czech Republic, France and Germany / 49-83 days after Visit 1 in Finland, Italy and Spain):

- A physical examination will be carried out.
- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- Administration of the second dose of the study vaccines (HRV vaccine or placebo).
- Administration of the second dose of the specific childhood vaccines.
- After vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.

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- You might be asked to complete the "Reactogenicity" diary card.
- You should complete the "unsolicited AE/medication" diary card.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 3 (30-48 days after Visit 2 in Finland and Italy / 49-83 days after Visit 2 in the Czech Republic, France, Germany and Spain):

- A physical examination will be carried out. ***(Physical examination at this visit can take place in case of request from the nurse or you, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- You might be asked for a blood sample (3 ml or 3/4 teaspoon) from your child/ward.
- During each gastroenteritis episode until the next visit, a “GE” diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 4 (at 7 months of age only for children from Spain):

Visit 4 is optional and may be combined with Visit 5. (**Amendment 1: 07 June 2005)**

- A physical examination will be carried out. ***(Physical examination at this visit can take place in case of request from the nurse or you, and can be limited appropriate with local requirements for routine physical examination for a child at this age***

Subject No._____ Date: _____

and appropriate for intervention that is to follow (blood draw etc.) **(Amendment 1: 07 June 2005)**

- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked for a blood sample (3 ml or 3/4 teaspoon) from your child/ward.
- You will return the completed diary card(s).
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 5 (mid-June to end-July 2005):

- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations (Finland and Italy) administered since the previous visit or contact.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- You should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 6 (at 12 months of age only for children from Italy OR at 13 months of age only for children from Finland who have provided blood samples at previous study visits):

Visit 6 is optional and may be combined with Visit 5. (**Amendment 1: 07 June 2005)**

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- A physical examination will be carried out. ***(Physical examination at this visit can take place in case of request from the nurse or you, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)*** **(Amendment 1: 07 June 2005)**
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked for a blood sample (3 ml or 3/4 teaspoon) from your child/ward.
- You will return the completed diary card(s).
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- You will be asked about any medications/vaccinations administered since the previous visit or contact.
- During each gastroenteritis episode until the next visit, a "GE" diary card should be completed.
- You should collect stool samples during each gastroenteritis episode and return them to the investigator on an ongoing basis.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.

Visit 7 (mid-June to end-July 2006):

- You will return the completed GE diary card.
- You will be asked if your child/ward manifested any signs or symptoms that you perceived as serious or if intussusception occurred since the previous visit or contact.
- If you child/ward drops out of the study due to an adverse event, you will be contacted to obtain information on that adverse event.
- Study end.

Risks associated with the study

Your child/ward will receive a combination vaccine (Infanrix Hexa®) to provide routinely recommended childhood vaccinations against six diseases in one injection. In France the second dose of the combination vaccine will be Infanrix Polio Hib®, in accordance with local immunization practices. If recommended by the local national Plan of Immunisation in your country, your child/ward may also receive vaccination against meningitis caused by Neisseria meningitidis C (e.g. Meningitec®) and/or severe bacterial infection caused by Streptococcus pneumoniae (e.g. Prevenar®) along with each HRV

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vaccine or placebo dose. These vaccines may cause side effects including pain and swelling at the injection site, high fever or crying.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, may occur, however, immediate medical assistance will be available following vaccination.

The HRV vaccine to be tested in this study has been shown to be safe in earlier studies with adults, children and infants. Few side effects such as mild fever, loose stools or vomiting have been reported. The vaccine will not cause the rotavirus disease.

Up to recently (as of 31 March 2004), serious illness associated with use of the HRV vaccine has been rare. In clinical trials with GSK Biologicals' HRV vaccine with over 74,450 infants enrolled, a total of 28 serious adverse events considered as possibly related to HRV vaccination have been reported. No deaths considered related to use of this HRV vaccine have occurred.

A vaccine based on a monkey (rhesus) strain of rotavirus was produced in the past in the USA by another company and it was noted after over a million doses had been administered that intussusception occurred very rarely as an illness in association with use of that vaccine. This product was subsequently taken off the market. Intussusception (telescoping of the intestine) is a spontaneous but rarely occurring event. As an example, in Finland it occurs in about 1 child in 2500 and there are about 15 cases of intussusception per year in children under 1 year of age.

In our studies (as of 18 May 2004) intussusception has been identified in 39 children in the entire HRV development program in which over 74,450 children have participated. For most of the cases it is not known if the children received HRV vaccine or placebo. An independent monitoring group reviews all cases, blinded (if the study is not finished) and unblinded (when the study is completed), on a regular basis and this board has up to May 2004 confirmed there are no concerns with the HRV vaccine. All intussusception cases were diagnosed promptly and treated immediately. These cases are considered to be coincidental and no conclusion regarding relationship with vaccination can be drawn from these cases at this time. It should be noted that GSK Biologicals' HRV vaccine is based on a **human** rotavirus and is different from RotaShield® vaccine that was based on a live rotavirus from monkeys.

The intussusception is usually quickly recognized and successfully treated. Your doctor and his/her staff will be well aware of the problem of intussusception and will take appropriate actions to evaluate and treat the condition. Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and high fever (even up to 41°C). The majority of intussusception cases resolve either spontaneously or can be treated effectively and completely with air

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contrast enemas. Surgical intervention is usually required in only a few cases. If you are interested, your doctor can provide you with more information regarding intussusception.

During the study, you should contact the investigator or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious or if intussusception occurs. If your child/ward has an intussusception, stool samples (or rectal swabs), throat swabs and blood samples from your child/ward will be collected to study its cause. If applicable, tissue specimens (such as intestinal resection specimens, lymphnodes, and the appendix) will be taken during the surgery.

You will be informed in a timely manner of any new findings developed during the course of this research study which might influence your decision on your child's/ward's participation to the trial.

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

There is no licensed rotavirus vaccine currently available for widely use.

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.

Joining this study is voluntary. If you decide not to join, there will be no penalty. You and your child/ward will lose no benefits.

Confidentiality and source document review

You understand and consent to the following:

It will be necessary for representatives of GlaxoSmithKline or possibly health authorities / drug regulatory agencies to access your child's/ward's medical records. Your child's/ward's participation in the study will be treated as confidential, that is, any personally identifiable information will be held and processed under secure conditions at GlaxoSmithKline (or an agent of GlaxoSmithKline) with access limited to appropriate GlaxoSmithKline staff or other authorized agents having a requirement to maintain the confidentiality of the information. Your child/ward will not be referred to by name in any report of the study. Your child's/ward's identity will not be disclosed to any person,

Subject No._____ Date: _____

except for the purposes described above and in the event of a medical emergency or if required by law.

Your child's/ward's data will be processed electronically to determine the outcome of this study, and to provide it to health authorities / drug regulatory agencies. Your child's/ward's data may be transferred to other countries (such as India, USA…) for these purposes GlaxoSmithKline 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 or scientific research purposes. If your child's/ward's data is used for any other purpose it will first be de-identified, that is all personally identifiable information will be removed, and will be processed in a de-identifiable form.

You may be entitled under law to access 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 your child/ward from the study at any time and you/he/she will be under no further obligation for any samplings or vaccinations.

Also, your child's participation in the study may be stopped or not initiated for any of the following reasons:

1. If you don't follow the investigator's instructions.
2. The investigator decides it is in the best interest of your child's health and welfare to discontinue.
3. There aren't enough patients in the study, or the study has reached the required number of patients.
4. GlaxoSmithKline Biologicals stops the study at this study site for other reasons not known now.

If you have any questions, please contact:

Name of investigator:

_____

Address of investigator:

_____

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_____

Telephone number of investigator: _____

Fax number of investigator: _____

Benefits of the study:

Your child/ward may have the benefit of being protected against rotavirus diseases. In addition, your child/ward will be offered a combination vaccination that provides immunization against up to six diseases in a single injection.

Blood samples taken from your child/ward will be used to determine if your child/ward has developed immunity to the study vaccine and the routine vaccines. Such tests are not normally done and are a benefit of participating in this study.

By participating in this study, you will help in the evaluation of this vaccine and ultimately may make it available for babies to protect them from rotavirus diseases.

There will be no charge for study-related doctor visits, examinations, and laboratory tests. All study vaccines will be provided free of charge.

Compensation:

If your child/ward 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 costs of such treatment will be paid for by GlaxoSmithKline Biologicals. All participants in the study are covered by global insurance policy contracted by GlaxoSmithKline 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: _____

_____

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Telephone number of investigator: _____

Fax number of investigator: _____

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etrack study number: 102247 (rota-036)

Subject No._____ Date: _____

Informed Consent

The HRV vaccine study has been clearly explained to me and I have read and understood the information provided. I agree that my [son/daughter/ward**] participates in the study. I understand that I have the right to decline that my son/daughter/ward enters the study and to withdraw her/him from it at any time for any reasons, without consequence to his/her present or future health care and attention which my child/ward 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)

Witness: _____
(if applicable)

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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)

Appendix 3F List of investigators and other important participants in the study

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof		FINLAND
CZECH REPUBLIC			
National Coordinating Principal Investigator	Ass. Prof.		
FINLAND			
National Coordinating Principal Investigator	Prof		FINLAND

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof [redacted]	[redacted]	[redacted] FINLAND
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof [redacted]	[redacted]	[redacted] FINLAND
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
FRANCE			
All centers (coordinating investigator)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof		FINLAND
GERMANY			
		Dr. med. Germany	
		Dr. med.	
		Dr. med. Germany	
		Dr. med. Germany	
	Dr.	Dr. med.	
		Dr. med. Germany	

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof		FINLAND
		Dr. med.	
		Germany	
		Dr. med.	
		Dr. med.	
		Drs.	
		Germany	
		Dr. med.	
		Dr. med.	
		Dr. med.	
		Dr. med.	
		Germany	
		Dr. med.	
		Dr. med.	
		Drs.	
		Dr. med.	
		Drs.	
		Drs.	
		Drs.	
		Dr. med.	
		Dr. med.	
		Dr. med.	
ITALY			

Centre Numbers*	Investigators	Investigational site	Location
Designated Principal Investigator for all centers in all countries	Prof [redacted]	[redacted]	[redacted] FINLAND
[redacted]	[redacted]	[redacted]	[redacted]
SPAIN			
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

†Prof. [redacted] was designated to oversee the study and approve the study report
GSK Biologicals assigned centre number

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Appendix 3G Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals
Clinical Research and Development

Investigator Approval Page

STUDY TITLE: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Study: 102247 (Rota-036) Development Phase: [IIIb]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:

Affiliation:

Signature of Investigator: _____

Date: _____

For internal use only
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GlaxoSmithKline Biologicals
Clinical Research and Development

Sponsor Signatory Approval Page

STUDY TITLE: A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.

Study: 102247 (Rota-036) Development Phase: [IIIb]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director

Signature: _____

Date: _____

For internal use only
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Appendix 3I Randomisation Scheme

RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_1 - Placebo Fi

Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag
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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_1 - Placebo Fi

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[redacted]																				

RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_1 - Placebo Fi

Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag	Trt. No	Bl. nb	Repl. flag
[redacted]																				

RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_1 - Placebo Fi

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_1 - HRV Fi

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_1 - HRV Fi

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_1 - HRV Fi

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_1 - HRV Fi

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_1 - HRV Fi

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

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RIX\ RDE\ ENABLE Randomisation list

ROTA-036 (A.10JAN2007)

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RIX\ RDE\ ENABLE

Randomisation list

ROTA-036 (A.10JAN2007)

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RIX\ RDE\ ENABLE   Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_2 - Placebo CR-Fr-Ge

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Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_2 - HRV CR-Fr-Ge

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Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_2 - HRV CR-Fr-Ge

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Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_2 - HRV CR-Fr-Ge

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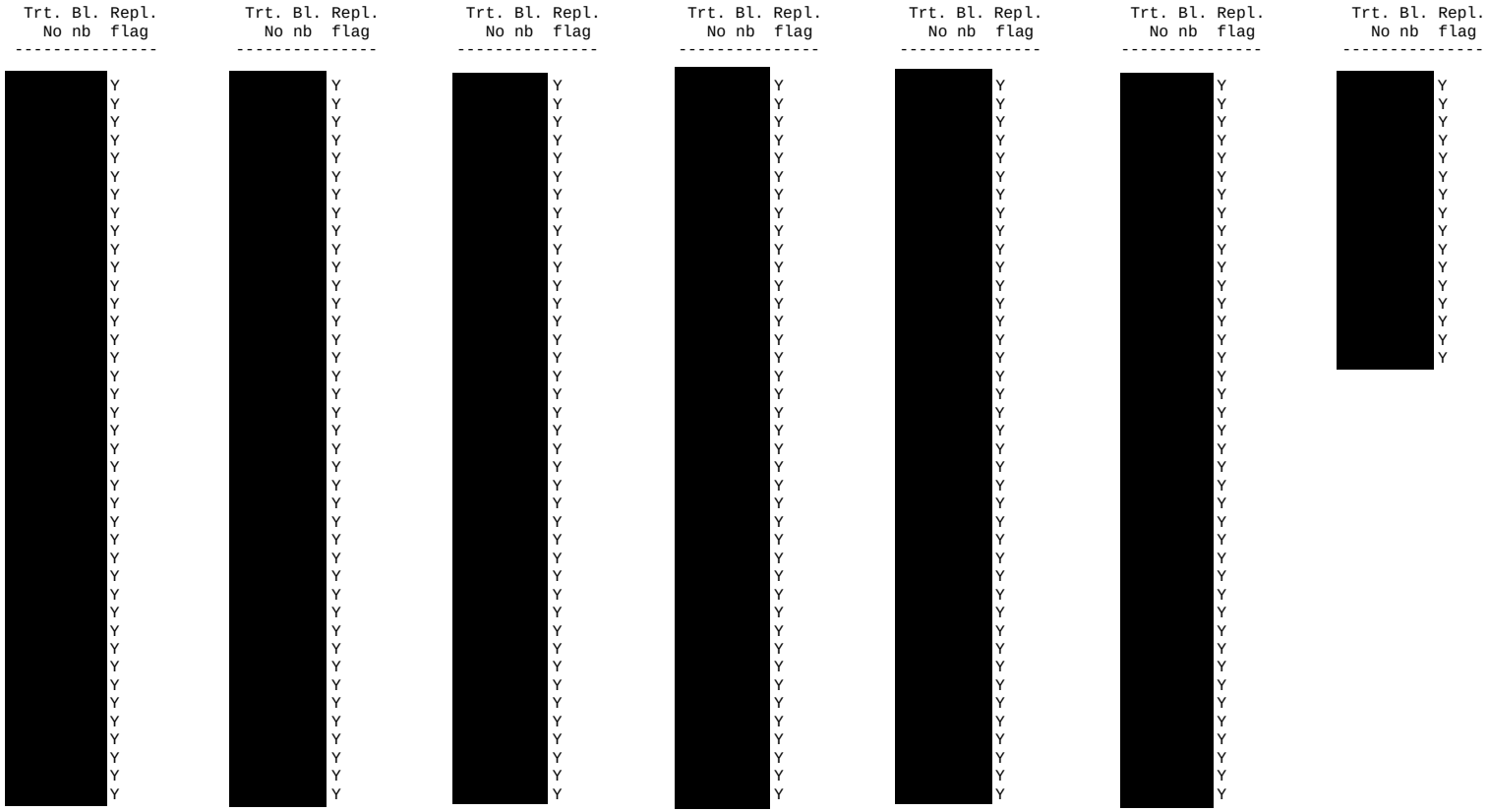
Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_2 - HRV CR-Fr-Ge



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Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_3 - Placebo Italy

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ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_3 - HRV Italy

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ROTA-036 (A.10JAN2007)

Subjects from Group : Pl_4 - Placebo Spain

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Randomisation list

ROTA-036 (A.10JAN2007)

Subjects from Group : HRV_4 - HRV Spain

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ROTA-036 (A.10JAN2007)

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Appendix 3J Audit Certificates

AUDIT CERTIFICATE

Report/Submission Number: 102247 (Rota/036)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312).

During the conduct and reporting of this study, the following independent audits were performed by or on behalf of GlaxoSmithKline.

Study Number	Audit Type	Auditor	Centre number	Country	Audit Date
102247 (Rota/036)	Investigator Site	[redacted]	[redacted]	Finland	13 April 2005
102247 (Rota/036)	Investigator Site			Finland	14 September 2005
102247 (Rota/036)	Investigator Site			Spain	25 October 2005
102247 (Rota/036)	Investigator Site			Germany	20 June 2006
102247 (Rota/036)	Investigator Site			France	12 Dec 2006
102247 (Rota/036)	Investigator Site			France	16 Dec 2006

Clinical Compliance hereby confirm that these audits detailed above were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

Name: [redacted] **Date:** 05 March 2007

Role: Director

European Clinical Compliance
GlaxoSmithKline Research and Development

Appendix 3M Publications based on the study

As of March 02 2007, there are no publications based on this study.

Appendix 3L Important publications referenced in the report

Appendix 3M CRFs for SAEs and withdrawals due to adverse events

This document is provided as 2 separate PDF files

- ROTA-036 (102247) CRFs for SAEs PART 1 (Annex)
- ROTA-036 (102247) CRFs for SAEs PART 2 (Annex)

GlaxoSmithKline Biologicals

Clinical Research & Development

Study Reporting and Analysis Plan Approval

Title:	A phase IIIb, double-blind, randomized, placebo-controlled, multi-country and multi-center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co-administration with specific childhood vaccines.
CPMS (e-Track) number – (alias):	444563 (Rota) 036 - Europe - 102247
Date:	3 November 2005
Co-ordinating authors:	[redacted]

Approved by:

Director **Clinical Development Manager**	Name: [redacted]	Signature	dd-mm-yyyy
Clinical Development Manager	Name: [redacted]	Signature	dd-mm-yyyy
Manager Bio-Statistician	Name: [redacted]	Signature	dd-mm-yyyy
Associate Director **Biometrics, Pediatric Vaccines**	Name: [redacted]	Signature	dd-mm-yyyy
Regulatory affairs	Name: [redacted]	Signature	dd-mm-yyyy

TABLE OF CONTENTS

LIST OF ABBEREVIATIONS

AE	Adverse event
ATP	According to protocol
CI	Confidence Interval
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EPI	Expanded Program of Immunization
GE	Gastroenteritis
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IS	Intussusception
LL	Lower limit
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase Chain Reaction
RDE	Remote Data Entry
RV	Rotavirus
SAE	Serious Adverse Event
UL	Upper limit
U/ml	Units per millilitre
VE	Vaccine efficacy

Glossary of terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Diarrhea:	Passage of three or more looser than normal stools within a day.
Eligible:	Qualified for enrolment 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 the according-to-protocol (ATP) analysis (see Section 6.2 for details on criteria for evaluability).
First Efficacy follow-up period:	Period starting from two weeks after Dose 2 of study vaccine or placebo and ending at Visit 5 (mid-June to end-July 2005).
Gastroenteritis:	Diarrhea with or without vomiting.
Rotavirus gastroenteritis (RV GE) for efficacy analysis (caused by the circulating wild-type rotavirus strain):	An episode of GE occurring at least two weeks after Dose 2 of study vaccine or placebo in which RV other than vaccine strain is identified in a stool sample collected during the episode of GE. 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 onset of the next GE episode, if subject had several episodes of GE

were considered.

Rotavirus season:	The rotavirus epidemic season is expected from beginning of December to end of May in Europe.
Second efficacy follow-up period:	Period starting on the day after Visit 5 and ending at Visit 7 (mid-June to end-July 2006).
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.
Severe rotavirus gastroenteritis:	An episode of RV GE with score ≥ 11 on a 20-point scoring system (Vesikari scoring system).
Solicited adverse event:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Subject:	Term used throughout the protocol to denote an individual that has been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject vaccinated before the Rotavirus season:	A subject will be considered as having been vaccinated before the rotavirus epidemic season if the day corresponding to two weeks after dose 2 is before December 1, 2005.
Subject vaccinated during the Rotavirus season:	A subject will be considered as having been vaccinated during the rotavirus epidemic season if the day corresponding to two weeks after dose 2 is between December 1, 2005 and May 31, 2005.
Unsolicited adverse event:	Any AE reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1. LIST OF AMENDMENTS TO THE RAP

Date	Description
3 November 2005	This study RAP prevails on the abridged RAP dated 27 June 2005. The abridged RAP dated 27 June 2005 was restricted to a description of the statistical analyses that were to be performed in the scope of an interim analysis as planned per protocol (see protocol amendment 1 dated 7 June 2005)

2. INTRODUCTION

This Study Reporting and Analysis Plan summarizes the 444563/036 (Rota-036) study features, as per protocol amendment 1 dated 7 June 2005 (sections 3-5) and the planned statistical analyses (section 6). The changes in the analyses as compared to the protocol/amendment are provided in section 7. A lay-out of the tables as they will be produced in the statistical report is available in annex 1.

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be limited to the statistician and the database administrator. The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 5.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed subsequently, and will be presented in an annex.

Analysis performed in the scope of an Interim analysis as planned per protocol have been described in an Abridged RAP dated 27 June 2005 (Please refer to section 6.5 for more details with regards to this interim analysis).

3. OBJECTIVES

3.1. Primary Objectives

- To determine the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

Definitions

GE: Diarrhea with or without vomiting.

Severe RV GE: An episode of RV GE with score ≥ 11 on a 20-point scoring system (Vesikari scale). An alternative scoring system will also be evaluated (Clark scale, see section 6.9).

Efficacy follow-up period: All subjects will be followed over two efficacy follow-up periods. Study enrolment will start September 2004. The first efficacy follow-up period will begin 2 weeks after Dose 2 of study vaccination and end at Visit 5 (mid-June to end-July 2005). The second efficacy follow-up period will begin on the day after Visit 5 and end at Visit 7 (mid-June to end-July 2006) covering approximately 12 months.

Refer to section 6.1 for the definition of primary endpoints

3.2. Secondary Objectives

Efficacy

First efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 until Visit 5.
- To assess vaccine efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season versus those who were vaccinated during the RV epidemic season.

Second efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Combined efficacy follow-up period

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by

the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with other specific childhood vaccinations against hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations against any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in the immunogenicity and reactogenicity subset, N=1800)

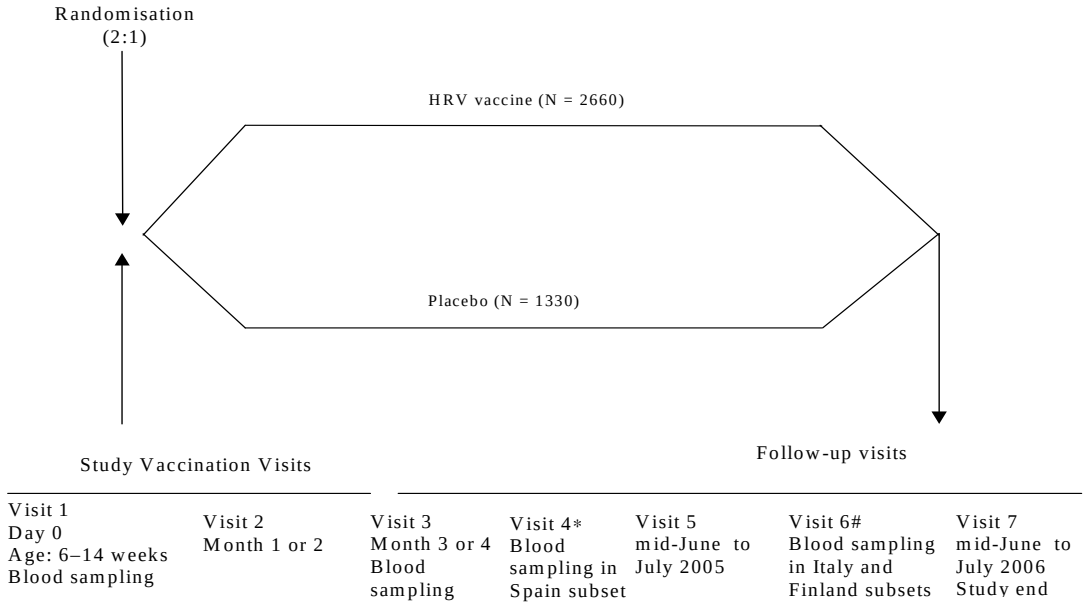
- To assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations 1 to 2 months after the second study vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine if any on the immune response to all antigens contained in each of the co-administered childhood vaccines (depending on the vaccination schedule in respective participating countries, Infanrix Hexa®, Infanrix Polio Hib®, Prevenar® or Meningitec® vaccines will be co-administered; in case of problems with availability of Meningetec® a similar alternative that is approved in Spain can be considered).

Safety and reactogenicity

- In the immunogenicity and reactogenicity subset (N=1800), to assess the reactogenicity of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of solicited symptoms.
- In all subjects, to assess the safety of two doses of GSK Biologicals' HRV vaccine given concomitantly with specific childhood vaccinations compared with placebo in terms of unsolicited AEs (31 days after each dose) and serious adverse events during the entire course of the study.

Refer to section 6.1 for the definition of secondary endpoints.

4. STUDY DESIGN OVERVIEW



*At 7 months of age only for subjects from Spain (optional).
#At 12 months of age only for subjects from Italy (optional). At 13 months of age only for subjects from Finland who are part of the "immunogenicity and reactogenicity subset" (optional).

- Experimental design: Double-blind, randomized, placebo-controlled, multi-country and multi-center study with two parallel groups.
- Control: Placebo (The placebo consist of all components of the study vaccine i.e. excipients and buffer, but no rotavirus particles).
- Blinding: Double-blind.
- Treatment allocation: Randomized (2:1 ratio).
- Treatment Groups:
  - Group HRV vaccine (N=2660): subjects will receive two doses of HRV vaccine co-administered with specific childhood vaccines
  - Group Placebo (N=1330): subjects will receive two doses of placebo co-administered with specific childhood vaccines
- The study vaccine and co-administered childhood vaccines will be given according to the local national Plan of Immunisation schedule in each country. The schedules in each participating country are as follows:

  Czech Republic: 3, 4, 5 months

Finland: 3, 5, 11-12 months
France and Germany: 2, 3, 4 months.
Italy: 3, 5, 11 months
Spain: 2, 4, 6 months

- Vaccination schedule: Immunization according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.
- Concomitant vaccinations:

➢ In accordance with the local national Plan of Immunisation schedule in the participating countries (see above), GSK Biologicals' Infanrix Hexa® [combination vaccine containing diphtheria and tetanus toxoids and acellular pertussis (DTPa), *Haemophilus influenzae* type b (Hib), Hepatitis B vaccine (HBV), and inactivated poliovirus vaccine (IPV)] will be administered with each HRV vaccine or placebo dose in the Czech Republic, Finland, Germany, Italy and Spain. In France, GSK Biologicals' Infanrix Hexa® will be administered with the first dose of HRV vaccine or placebo and GSK Biologicals' Infanrix Polio Hib® [combination vaccine containing DTPa, Hib and IPV] will be administered with the second dose of HRV vaccine or placebo; the third dose of the routine childhood series will be Infanrix Hexa®, following national immunization practices.

➢ In addition to the routine combination vaccine, the following vaccines will be co-administered with each HRV vaccine or placebo dose in the specified countries as part of the local national Plan of Immunization schedule:

- Vaccine against *Neisseria meningitidis* C (e.g. Meningitec® or similar licensed vaccine) will be co-administered in Spain.
- Vaccine against *Streptococcus pneumoniae* (e.g. Prevenar®) will be administered in France and Germany.

Thereafter, routine vaccinations will be given as per the recommended respective national Plan of Immunisation schedule of each country.

- Study visits: All subjects will have five study visits (Visits 1, 2, 3, 5 and 7). Subjects from the "immunogenicity and reactogenicity subset" in Spain may have if necessary one additional visit (Visit 4). Subjects from the "immunogenicity and reactogenicity subset" in Finland and in Italy may have if necessary one additional visit (Visit 6).

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=1800), Dose 1 (HRV vaccine or placebo) and Dose 1 specific childhood vaccines.

  Visit 2 (Month 1 or 2) – Dose 2 (HRV vaccine or placebo), Dose 2 specific childhood vaccines, follow-up for reactogenicity (in a subset of subjects, N=1800) with return of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

  Visit 3 (Month 3 or 4) – Post-vaccination blood sample from a subset of subjects (N=1800), follow-up for reactogenicity (in a subset of subjects, N=1800) with return

of reactogenicity diary cards, follow-up for GE episodes with return of any GE cards and follow-up for safety.

Administration of the Dose 3 of specific childhood vaccines is not marked as a study visit. Dose 3 of specific childhood vaccines should be given as indicated in the national Plan of Immunisation schedule of the respective countries.

Since the blood sampling time point one month post Dose 3 of the childhood vaccines does not always coincide with study visits planned for all subjects, subjects from Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset" may have if necessary an additional study visit for blood sampling to evaluate immunogenicity of routine vaccines. The additional study visit will take place one month after the third dose of the primary vaccination course in each country: Visit 4 will take place at 7 months of age in Spain; Visit 6 will take place in Italy (at 12 months of age) and Finland (at 13 months of age). Subjects in the Czech Republic, France and Germany will not require a separate visit since the blood sampling at post Dose 3 of the childhood vaccines coincides with Visit 3.

Visit 4 ("immunogenicity and reactogenicity subset" in Spain only) one month after the third dose of the primary vaccination course at 7 months of age – Post-vaccination blood sample from all subjects in Spain (N=300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 5 (mid-June to end-July 2005) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit 5 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Visit 6 ("immunogenicity and reactogenicity subset" in Italy and Finland only) one month after the third dose of the primary vaccination course

In Italy: Visit 6 at 12 months of age – Post-vaccination blood sample from all subjects in Italy (N= 300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

In Finland: Visit 6 at 13 months of age – Post-vaccination blood sample from a subset of subjects (N= 300), follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs).

Visit 7 (mid-June to end-July 2006) – Follow-up for GE episodes with return of any GE cards and follow-up for safety (SAEs) and study conclusion.

- Active follow-up for occurrence of GE episodes will be conducted during the period starting from administration of Dose 1 until the last visit planned for the subject.

From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005, the intention is to make contact with each subject's parent/guardian on an approximately weekly basis to check on the occurrence of any GE. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or another convenient means. From June 2005 onwards, the intention is that this contact will take place approximately every two weeks until 1 December 2005. Weekly contact will be resumed again during the second RV epidemic season after study vaccination (December 2005 to end of May 2006). Approximately bi-weekly contact will take place from June 2006 until study end. All contacts will be logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt will be made before the next planned contact.

For each GE episode occurring during the study period, a GE diary card should be completed daily until end of the GE symptoms. During each GE episode, a stool sample(s) should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms.

- Specific solicited symptoms occurring during the 8-day follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo will be recorded by parents/guardians of a subset of subjects (N=1800) using diary cards. Unsolicited symptoms occurring within 31 days (Day 0-Day 30) after each study vaccine dose and SAEs during the entire study period will be recorded in all subjects. Parents/guardians will be asked to contact the investigator or his/her delegate in case of SAEs or IS during the study. Parents/guardians will be asked regarding occurrence of SAEs or IS at each contact during the study (at planned study visits as well as contact through telephone call, SMS using cellular phone, an Independent Calling Centre or other convenient means).
- An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/IS case is reviewed by this committee.
- Duration of the study: Study subjects will be followed until mid-June to end-July 2006. The intended duration of the study, per subject, will not exceed a total of maximum of 24 months.
- Data collection: Remote Data Entry (RDE).

5. CONDUCT OF STUDY

5.1. Outline of study procedures

Table 1 List of study procedures at visits planned for all subjects in all countries

Age **Visit §** **Timing** **Sampling timepoint**	**6-14 weeks** **VISIT 1** **Day 0** **Pre**	**VISIT 2** **Month 1 or 2**	**VISIT 3** **Month 3 or 4** **Post vacc 2**	**VISIT 5**	**VISIT 7**
Informed consent	●				
Check inclusion criteria	●				
Check exclusion criteria	●				
Check elimination criteria		●	●	●	●
Check contraindications	●	●			
Medical history	●				
Physical examination	●	●	●‡		
Pre-vaccination body temperature	●	●			
Measure/record height and weight	●				
Record feeding practice	●	●			
Randomization	●				
Blood sampling in a subset: for antibody determination	● (1 ml) (N=1800)		● (3 ml) (N=1800)		
Study vaccination (HRV or placebo)	●	●			
Co-administration of childhood vaccinations∗	●	●			
Recording all childhood vaccinations	●	●	●	● Finland/Italy only	
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)	●	●			
Return of reactogenicity diary cards in a subset (N=1800)		●	●		
Transcription of the reactogenicity diary card in a subset (N=1800)		●	●		
Return of unsolicited AE/medication diary card from all subjects		●	●		
Record any concomitant medication/vaccination#	●	●	●	●	
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●		
Reporting of SAEs in all subjects	●	●	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●	●	●
Contact¶ for GE and safety follow-up	●	●	●	●	●
Return of GE diary card		●	●	●	●
GE diary card transcription		●	●	●	●

Collection of stool samples if subjects has GE	●	●	●	●	●
Study conclusion				●	
Study end					●

§Additional visits can be planned if necessary for subjects in Spain, Italy and Finland who are part of the "immunogenicity and reactogenicity subset": Visit 4 will take place in Spain only and Visit 6 take place in Finland and Italy only. Visit 4 and Visit 6 are not applicable for France, Germany and the Czech Republic. Refer to Table 2 for more details Note: The double-line border following Month 3 indicates the interim analysis which will be performed on the immunogenicity and reactogenicity data obtained after completion of Visit 3.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)

∗ The third dose of the routine childhood vaccine(s) must be given according to the respective national Immunisation plans of each country. A study visit is not planned specifically for administration of third dose of the routine childhood vaccine(s).

#According to guidelines specified in Section 6.9 of the protocol

¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

Table 2 List of study procedures at *optional* additional visits planned for subjects in Spain (Visit 4), Italy (Visit 6) and Finland (Visit 6) who are part of the "immunogenicity and reactogenicity subset"

Age **Visit** **Timing** **Sampling timepoint**	**VISIT 4** **SPAIN only** **Month 5** **Post-vacc 2**∗	**VISIT 6** **ITALY only** **Month 9** **Post-vacc 2**∗	 **FINLAND only** **Month 10** **Post-vacc 2**∗
Informed consent			
Check inclusion criteria			
Check exclusion criteria			
Check elimination criteria	●	●	●
Check contraindications			
Medical history			
Physical examination	●‡	●‡	●‡
Pre-vaccination body temperature			
Measure/record height and weight			
Record feeding practice			
Randomization			
Blood sampling in a subset: for antibody determination (3 ml)	● (target N=300 from Spain)	● (target N=300 from Italy)	● (target N=300 from Finland)
Study vaccination (HRV or placebo)			
Co-administration of childhood vaccinations			
Recording all childhood vaccinations	●	●	●
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians in a subset (N=1800)			
Return of reactogenicity diary cards in a subset (N=1800)			
Transcription of the reactogenicity diary card in a subset (N=1800)			
Return of unsolicited AE/medication diary card from all subjects			
Record any concomitant medication/vaccination#	●	●	●
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator			
Reporting of SAEs in all subjects	●	●	●
Reporting AEs leading to drop out in all subjects	●	●	●
Contact¶ for GE and safety follow-up	●	●	●
Return of GE diary card	●	●	●
GE diary card transcription	●	●	●
Collection of stool samples if subjects has GE	●	●	●
Study conclusion			
Study end			

● is used to indicate a study procedure that requires documentation in the individual eCRF.

∗The sampling time point is post Dose 2 of HRV vaccine or placebo and post Dose 3 of routine childhood vaccinations.
‡ Physical examination at this visit can take place in case of request from the nurse or parents/guardians, and can be limited appropriate with local requirements for routine physical examination for a child at this age and appropriate for intervention that is to follow (blood draw etc.)
#According to guidelines specified in Section 6.9 of the protocol
¶Frequency of contact: From Day 7 after Dose 1 of HRV vaccine or placebo until end of May 2005: weekly. From June 2005 until 1 December 2005: bi-weekly. From December 2005 until end of May 2006: weekly. June 2006 until study end: bi-weekly.

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject's evaluability in the according to protocol analyses (see section 6.2 for details of criteria for evaluability and cohorts to be analyzed).

The local national Plan of Immunization schedules vary from country to country. The local immunization schedule should be followed to administer study vaccine concomitantly with specific childhood vaccinations at Visit 1 and Visit 2. In order to assess the safety of the study vaccine, the interval between two study vaccine doses should not be less than 30 days. Table 3 presents the interval between study visits to be followed in each specified country. Table 4 presents the age at each visit per country.

Table 3 Intervals between study visits

Protocol interval					
Interval	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Routine schedule	**3, 4, 5 months**	**3, 5, 11-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	30-48 days	49-83 days	30-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	30-48 days	49-83 days	30-48 days	49-83 days
Visit 3-Visit 4	Not applicable				30-48 days after the third dose of childhood vaccines
End of the 1st efficacy follow-up period	mid-June to end-July 2005				
one month after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable	30-48 days after the third dose of childhood vaccines	Not applicable
End of the 2nd efficacy follow-up period	mid-June to end-July 2006				

Adapted interval					
Interval	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Routine schedule	**3, 4, 5 months**	**3, 5, 11-12 months**	**2, 3, 4 months**	**3, 5, 11 months**	**2, 4, 6 months**
Visit 1-Visit 2	21-48 days	49-83 days	21-48 days	49-83 days	49-83 days
Visit 2-Visit 3	49-83 days	21-48 days	49-83 days	21-48 days	49-83 days
Visit 3-Visit 4	No subjects will be eliminated for not respecting these time intervals				
End of the 1st efficacy follow-up period					
one month after the third dose of childhood vaccines					
End of the 2nd efficacy follow-up period					

Table 4 Age of the subjects at each study visits

Age at Visit	**Czech Republic**	**Finland**	**France and Germany**	**Italy**	**Spain**
Visit 1	3 months	3 months	2 months	3 months	2 months
Visit 2	4 months	5 months	3 months	5 months	4 months
Visit 3	6 months	6 months	5 months	6 months	6 months
Visit 4	Not applicable				7 months
Visit 5	Will vary (Visit to be completed by mid-June to end-July 2005)				
Visit 6	Not applicable	13 months	Not applicable	12 months	Not applicable
Visit 7	Will vary (Visit to be completed by mid-June to end-July 2006)				

5.2. Laboratory assays

5.2.1. GE stool analysis

Stool samples collected during GE episodes will be processed at the study site and shipped frozen to GSK Biologicals, Belgium for further distribution to the core laboratories where analysis will be performed.

All GE stool samples will be analysed at GSK Biologicals, Rixensart, Belgium to detect RV antigen using Enzyme Linked Immunosorbent Assay (RotaClone assay from Meridian Bioscience, USA). If a stool sample tests positive for RV, the sample will be tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridization assay at Delft Diagnostic Laboratory, the Netherlands to determine the G serotype and the P genotype. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV.

Any additional testing on stool samples will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine

5.2.2. Serum analysis

A subset of 1800 subjects (target of 300 subjects per country) will provide blood samples. Blood samples collected at each sampling time point will be centrifuged and the separated serum should be stored at –20°C until shipped to the sponsor for analysis.

All serological assays will be performed at GSK Biologicals, Rixensart, Belgium.

Anti-rotavirus IgA antibody concentrations will be measured in all serum samples collected at Visit 1 and Visit 3.

Other assays will be performed depending on the specific vaccines co-administered with each HRV vaccine or placebo dose. Antibodies to all antigens contained in the co-administered vaccines will be measured at each sampling time point [i.e. Visit 3 (all countries), Visit 4 (Spain) and Visit 6 (Italy and Finland)]. In case of insufficient sample analysis will be conducted with priority to: rotavirus, meningococcal C bactericidal activity and ELISA test, antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.

Table 5 summarizes the laboratory assays to be performed on the serum samples.

Table 5 Laboratory Assays

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off
rotavirus	IgA ELISA	in-house	U/ml	20
anti-D	ELISA	in-house	IU/ml	0.1
anti-T	ELISA	in-house	IU/ml	0.1
anti-PT	ELISA	in-house	EL.U/ml	5
anti-FHA	ELISA	in-house	EL.U/ml	5
anti-PRN	ELISA	in-house	EL.U/ml	5
anti-HBs	ELISA	in-house	mIU/ml	10
anti-poliovirus type 1	micro-neutralization test	in-house	ED50	8
anti-poliovirus type 2	micro-neutralization test	in-house	ED50	8
anti-poliovirus type 3	micro-neutralization test	in-house	ED50	8
anti-PRP	ELISA	in-house	µg/ml	0.15
Meningococcal C bactericidal activity#	Serum bactericidal test	in-house	Dilution	1/8
	ELISA	In-house	µg/ml	0.3
Antibodies against 7 serotypes (4, 9V,14, 18C, 23 F, 6B, 19F) of pnemococcal capsular polysaccharide*	ELISA	in-house	µg/ml	0.05

U = units
IU = International units

EL.U = Elisa units
ED 50 = Estimated dose 50%
#For samples from Spain only
*For samples from France and Germany only

Any additional testing on serum samples will be performed if deemed necessary by GSK Biologicals if any findings concerning toxicity or immunogenicity in the present study or in other studies necessitate further investigations.

5.2.3. IS samples

Refer to Appendix H of protocol amendment 1 dated 7 June 2005 for information on analysis of biological samples collected for IS.

The GSK Biologicals' designated laboratories will test:

- Frozen stool samples or rectal swab and throat swab specimens by RT-PCR to determine the presence of RV, enteroviruses and adenoviruses.

- Acute and convalescent blood samples will be tested to detect an acute antibody response to RV. Blood and/or stool and/or throat swab tests will be tested for the presence of a range of suspected pathogens. Also, histopathology evaluation of tissue will be conducted.

- In case of surgical resection, a surgical specimen of any enlarged mesenteric lymph node should be obtained. If bowel or the appendix is resected, these specimens also should be included in the evaluation. As molecular assays are to be performed on these surgical specimens, the use of powderless gloves, RNAse-free pipettes, aerosol RNAse-free tips, non-autoclaved disposable plasticware/forceps, commercial PBS solution/water/Formaldehyde solutions as well as limited steps of the solution preparation are highly recommended to avoid RNAse contamination. Refer to the lab workbook for the process of resected tissue. Testing including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR will be arranged by GSK Biologicals in consultation with the Attending Pathologist.

- Fresh stool samples may be tested locally according to standard microbiologic methods for the presence of any suspected enteric pathogens, e.g. Salmonella, Shigella, Campylobacter, Yersinia, and others.

Any additional testing on biological samples collected for IS will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine.

5.2.4. Serology and stool analysis plan

Table 6 presents the plan for analyses of serum and stool samples collected during the study.

Table 6 Serology and Stool Analysis Plan

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times during the study			RV	all	none
Serology					
Pre	0	1	HRV	Immunogenicity subset (N=1800)	none
Post-vacc 2∗	3	3	HRV, 7 *S. pneumoniae* serotypes (France and Germany only) , D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP,	Immunogenicity subset except Spain (N=1500)	HRV, 7 *S. pneumoniae* serotypes (France and Germany only), D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	4	3	HRV, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test (Spain only)	N=300 from Spain	HRV, Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
Post-vacc 2#	5	4 (Spain only)	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP and Men C serum bactericidal activity and ELISA test	N=300 from Spain	Men C serum bactericidal activity and ELISA test, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, and PRP.
	9	6 (Italy only)	, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP	N=300 from Italy	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP
	10	6 (Finland only)	, D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP	N=300 from Finland	D, T, PT, FHA, PRN, HBs, poliovirus serotypes 1, 2 and 3, PRP

∗Post Dose 2 of study vaccine for all countries. Depending on the local national Plan of Immunisation schedule in each country, may be post Dose 2 or post Dose 3 of routine childhood vaccines

#Corresponds to Post Dose 3 of routine childhood vaccines in the respective countries.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to the priority ranking specified in Table 6.

5.3. Adverse events

5.3.1. Solicited general AEs

Information on solicited symptoms will be collected for 8 days (Day 0 to Day 7) after each HRV vaccine or placebo dose by the parents/guardians of a subset of subjects (N=1800) using diary cards provided by the sponsor. Table 7 specifies the general AEs solicited during this study.

Table 7 Solicited general adverse events

Fever (Rectal/Axillary)
Fussiness/Irritability
Loss of appetite
Vomiting
Diarrhea
Cough/runny nose

N.B. Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded.

5.3.2. Unsolicited AEs

All AEs occurring within 31 days following administration of each dose of vaccine/ placebo will be recorded on the eCRF.

All AEs leading to subject withdrawal or drop out will be recorded on eCRF.

All SAEs occurring during the study period will be recorded on the eCRF.

5.3.3. Assessment of intensity

Intensity of the following AEs will be assessed as described in Table 8.

Table 8 Intensity scales to be used by parents/guardians for solicited symptoms

Adverse Experience	Intensity grade	Parameter
Fever*		Record temperature in °C using a rectal/axillary 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
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 temperature ≥38°C (≥37.5°C) as measured by a rectal (axillary) thermometer.
¶Diarrhea is defined as passage of 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.

The maximum intensity of diarrhea, fever and vomiting occurring during the solicited 8-day follow-up period will be scored at GSK Biologicals as shown in Table 9.

Table 9 Intensity scales used at GSK Biologicals for diarrhea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	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
Fever	0	Rectal temperature < 38.0°C or axillary temperature < 37.5°C
	1	Rectal temperature ≥ 38.0 – ≤ 38.5°C or axillary temperature ≥ 37.5 – ≤ 38.0°C
	2	Rectal temperature > 38.5 – ≤ 39.5°C or axillary temperature > 38.0 – ≤ 39.0°C
	3	Rectal temperature > 39.5°C or axillary temperature > 39.0°C

The investigator will make an assessment of intensity for all other AEs, i.e. unsolicited symptoms reported within 31 days (Day 0-Day 31) after each study vaccine dose and AEs leading to drop out or SAEs reported during the study. The assessment will be based

on the investigator's clinical judgement. The intensity of each AE (unsolicited symptoms or AE leading to drop out) and SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities. (In a young child, such an AE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in section 8.2 of protocol amendment 1 dated 7 June 2005.

5.3.4. Assessment of causality

Causality of all AE and SAEs is assessed by the investigator using the following two categories:

NO	:	The AE 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 AE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the AE.

5.3.5. GE episodes

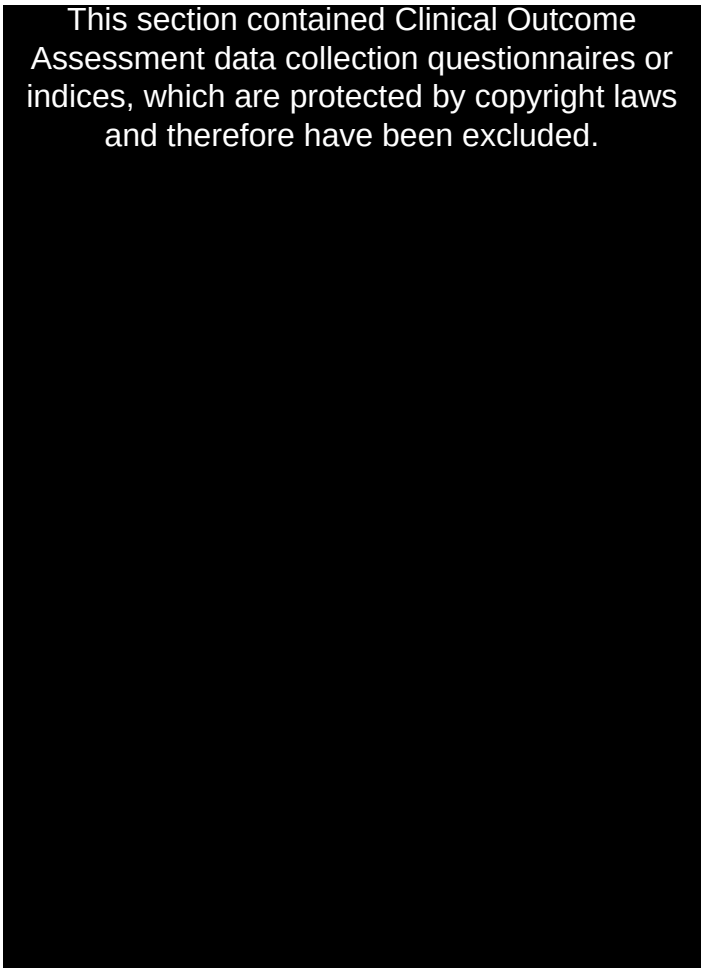
All subjects will be followed for GE episode of any etiology (defined as diarrhea with or without vomiting) starting from Dose 1 up to study end (Visit 7). Stool samples will be collected during each GE episode (see Section 6.3.2 for the allowed interval for stools collection).

5.3.5.1. Vesikari scale

Any GE episode starting from Dose 1 up to study end should be documented using diary card. The following information will be collected on the diary card during each GE episode: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be also recorded. The information collected on the GE diary card will allow the assessment of the intensity of each GE episode using the Vesikari 20-point scoring system [Ruuska, 1990].

In the Vesikari 20-point scoring system [Ruuska, 1990], points will be assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, the treatment given or hospitalization for each episode of GE as shown in Table 10.

Table 10 The Vesikari 20-point scoring system to determine the intensity of GE episodes reported during the study



∗ The highest temperature recorded during the episode will be scored.
§ missing confirmed correspond to the situation where the route for temperature is omitted in the eCRF and has not been recovered while addressing queries to the investigator

For each episode of GE, a global score (sum of individual points) is calculated.

The severity using the 20-points Vesikari scale is defined as below:

- A global score <7 is prospectively defined as mild,
- A global score between 7 and 10 is prospectively defined as moderate,
- A global score ≥11 is prospectively defined as severe [Ruuska, 1990].

5.3.5.2. Clark scale

In addition to the information collected for the assessment of the intensity of each GE episode using the Vesikari 20-point scoring system [Ruuska, 1990], behavioural symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the diary cards. This additional information will allow exploratory analysis of the Clark 24-point scoring system [Clark, 1988].

In the Clark 24-point scoring [Clark, 1988] points will be assigned at GSK Biologicals according to duration and intensity of diarrhea, vomiting and fever, as well as on the intensity and duration of behavior symptoms as shown in Table 11.

Table 11 The Clark 24-point scoring system to determine the intensity of GE episodes reported during the study

Adverse Experience		**Points**
Duration of looser than normal stools (days)		
1-4		1
5-7		2
> 7		3
Maximum number of looser than normal stools /24 hours		
2-4		1
5-7		2
> 7		3
Duration of vomiting (days)		
2		1
3-5		2
> 5		3
Maximum number of episodes of vomiting/24 hours		
1-3		1
4-6		2
> 6		3
Fever		
Rectally*	**Axillary/missing confirmed§***	
38.0 – 38.2°C	37.5– 37.7°C	1
38.3 – 38.7°C	37.8– 38.2°C	2
≥ 38.8°C	≥ 38.3°C	3
Duration of fever (days)		

1-2	1
3-4	2
≥ 5	3
Behavioral symptoms	
Irritable/less playful	1
Lethargic/listless	2
Seizures	3
Duration of behavioral symptoms	
1-2	1
3-4	2
≥ 5	3

∗ The highest temperature recorded during the episode will be scored.
§ missing confirmed correspond to the situation where the route for temperature is omitted in the eCRF and has not been recovered while addressing queries to the investigator

The severity using the 24-points Clark scale is defined as below:

- A global score < 9 is prospectively defined as mild,
- A global score between 9 and 16 is prospectively defined as moderate,
- A global score > 16 is prospectively defined as severe .

6. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

6.1. Endpoints

6.1.1. Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

6.1.2. Secondary endpoints

Efficacy during the first efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the first efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.

- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 5.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season.
- Occurrence of any and severe RV GE caused by the circulating wild-type RV strains during the first efficacy follow-up period in subjects who were vaccinated during the RV epidemic season.

Efficacy during the second efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the second efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the second efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the second efficacy follow-up period.

Efficacy during the combined efficacy follow-up period

- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the combined efficacy follow-up period.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotypes during the combined efficacy follow-up period.
- Occurrence of hospitalization due to RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.
- Occurrence of any medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) for RV GE caused by the circulating wild-type RV strains during the combined efficacy follow-up period.

Immunogenicity (in a subset of subjects, N=1800)

- Serum rotavirus IgA antibody concentration expressed as GMC at Visit 1 and Visit 3.

- Seroconversion rates to anti-rotavirus IgA antibody at Visit 3.
- Serum levels of antibodies to all antigens contained in each of the different childhood vaccines at Visit 3 and Visit 4 or Visit 6 (if applicable):
  - Serum concentration/titer expressed as GMC/Ts for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus serotypes 1, 2 and 3, anti-PRP, anti-HBs, anti-Men C or antibodies to the 7 Streptococcus pneumoniae serotypes.
  - Seroprotection status:
    - anti-diphtheria antibody concentrations ≥ 0.1 IU/ml
    - anti-tetanus antibody concentrations ≥ 0.1 IU/ml
    - anti-polio type 1 antibody titers ≥ 8
    - anti-polio type 2 antibody titers ≥ 8
    - anti-polio type 3 antibody titers ≥ 8
    - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 μg/ml
    - anti-HBs antibody concentrations ≥ 10.0 mIU/ml
    - *Neisseria meningitidis* C serum bactericidal activity titer ≥ 1/8
    - anti Neisseria meningitidis antibody concentrations (ELISA) ≥ 0.3 μg/ml
    - antibody concentrations to Streptococcus pneumoniae serotypes 4, 9V,14, 18C, 23 F, 6B, 19F ≥ 0.05 μg/ml
  - Seropositivity status:
    - anti-PT antibody concentrations ≥ 5 EL.U/ml
    - anti-FHA antibody concentrations ≥ 5 EL.U/ml
    - anti-PRN antibody concentrations ≥ 5 EL.U/ml

Safety and reactogenicity

- In a subset of subjects (N=1800), occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after each dose of HRV vaccine or placebo co-administered with childhood vaccines.
- For all subjects, occurrence of unsolicited symptoms within 31 days (Day 0 to Day 30) after each dose of HRV vaccine or placebo co-administered with childhood vaccines, according to the MedDRA classification.
- For all subjects, occurrence of serious adverse events throughout the entire study period.

6.2. Study cohorts

Five cohorts will be evaluated, as described below. The target enrolment (number of subjects) is also presented.

6.2.1. Number of subjects /centres

Total target enrolment will be 3990 subjects (2660 subjects in the HRV vaccine group and 1330 subjects in the placebo group). Refer to Section 10.3 of protocol amendment 1 dated 7 June 2005 for a detailed description of the criteria used in the estimation of sample size.

All enrolled subjects will be followed for efficacy and safety.

Subjects will be enrolled at multiple sites in up to six European Union countries (Czech Republic, France, Finland, Germany, Italy and Spain). A target total of 2490 subjects will be enrolled in Finland. A target total of 300 subjects will be enrolled in each of the remaining five countries. In case any countries would fall behind in subject recruitment, a redistribution of the target numbers can be considered in the later part of the enrolment period by allowing any of the other participating countries to enrol additional subjects in an effort to ensure full enrolment up to the maximum of 3990 subjects allowed in this study.

A subset of 1800 subjects (target 300 subjects per country) will be part of the "immunogenicity and reactogenicity subset". All subjects in this subset will provide blood samples to evaluate immunogenicity of study vaccine and concomitantly administered childhood vaccines. Data on specific solicited symptoms during the eight-day (Day 0 to Day 7) follow-up period after each study vaccine dose will be collected for this subset.

For Finland, 300 subjects enrolled at specific centre(s) will be part of the "immunogenicity and reactogenicity subset". For each of the other participating countries, all of the 300 enrolled subjects will be part of the "immunogenicity and reactogenicity subset".

Enrolment will be terminated when 3990 subjects have been enrolled.

6.2.2. Total vaccinated cohort

The total vaccinated cohort will include all subjects with at least one vaccine administration documented:

- a safety analysis based on the total vaccinated cohort will include all vaccinated subjects
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects.

6.2.3. Total Vaccinated cohort for the reactogenicity and immunogenicity subset

The total vaccinated cohort for the reactogenicity and immunogenicity subset will include all subjects with at least one vaccine administration documented and for whom solicited symptoms and blood samples were to be collected:

- a reactogenicity analysis based on the total vaccinated cohort for the reactogenicity and immunogenicity subset will include all vaccinated subjects for whom solicited symptoms were to be collected
- an immunogenicity analysis based on the total vaccinated cohort for the reactogenicity and immunogenicity subset will include all vaccinated subjects for whom immunogenicity data are available.

6.2.4. ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects:

- who received 2 doses of HRV vaccine or placebo according to their random assignment,
- who have entered into the efficacy surveillance period:
  - have follow-up beyond 2 weeks after Dose 2 of study vaccination for the analysis of the first efficacy follow-up period,
  - have follow-up beyond the end of the first efficacy follow-up period for the analysis of the second efficacy follow-up period,
  - have follow-up beyond 2 weeks after Dose 2 of study vaccination for analysis of the combined efficacy follow-up periods.
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 was administered and 2 weeks after Dose 2 of HRV vaccine or placebo was administered.
- for whom the randomization code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol

Annex 2 details the elimination code that will be used to identify subjects to be excluded from the ATP cohort for efficacy.

6.2.5. ATP cohort for reactogenicity

The ATP cohort for reactogenicity will include all vaccinated subjects for whom solicited symptoms were to be collected and

- who have received at least one dose of study vaccine/control according to their random assignment,

- for whom the randomization code has not been broken,
- who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind replacement".
- who have not received a vaccine forbidden by or not specified in the protocol.
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of dose 1.

Annex 2 details the elimination code that will be used to identify subjects to be excluded from the ATP cohort for reactogenicity.

6.2.6. ATP cohort for immunogenicity

The ATP cohort for immunogenicity will include all subjects from the ATP cohort for reactogenicity:

- who have 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 comply with vaccination schedule for HRV vaccine or placebo,
- who comply with blood sampling schedule,
- for whom immunogenicity data are available, at pre and post sampling timepoint for anti-rotavirus IgA antibody.
- who have no rotavirus other than vaccine strain in GE stool samples collected up to Visit 3.
- who have no concomitant infection unrelated to the vaccine which may influence the immune response.

Annex 2 details the elimination code that will be used to identify subjects to be excluded from the ATP cohort for immunogenicity.

6.2.7. Analysis cohort

Efficacy

The ATP cohort for efficacy will be used for the primary analysis of efficacy. A secondary analysis of efficacy based on the total vaccinated cohort will also be performed.

Reactogencitiy/Safety

The total vaccinated cohort for reactogenicity and immunogenicity subset will be used for the primary analysis of reactogenicity. Unsolicited adverse events will also be presented for the total vaccinated cohort (for Finland and pooled countries). The analysis on the ATP cohort for reactogenicity will only be performed if more than 5% of the subjects from the the total vaccinated cohort for reactogenicity and immunogenicity subset are excluded from the ATP cohort for reactogenicity.

Immunogenicity

The ATP cohort for immunogenicity will be used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort cohort for reactogenicity and immunogenicity subset will only be performed if more than 5% of the vaccinated subjects with immunological results are excluded from the ATP cohort for immunogenicity. In such a case, the total vaccinated cohort for reactogenicity and immunogenicity subset analyses evaluate whether exclusion from the ATP cohort have biased the results.

The list of applicable elimination codes for each cohort can be found in Annex 2.

Cohort	**Elimination codes**
Total vaccinated cohort	1010-1030
Total vaccinated cohort for the reactogenicity and immunogencity subset	1010-1035
ATP cohort for reactogenicity	1010-1500
ATP cohort for immunogenicity	1010-2500
ATP cohort for efficacy year-1	1010-1500; 3010-3500 but including subject who have only been given code 1035
ATP cohort for efficacy year-2	1010-1500; 3010-3500; 4020 but including subject who have only been given code 1035

6.3. Derived and transformed data

6.3.1. Demographic variables

Height demographic characteristics are investigated:

(1) age (in weeks) at the first vaccine dose (continuous variable),

(2) age (in weeks) at the second vaccine dose (continuous variable),
(3) gender (binary variable),
(4) race (categorical variable),
(5) height (in cm) at Visit 1 (continuous variable),
(6) weight (in kg) at Visit 1 (continuous variable),
(7) BMI (in kg/m²) at Visit 1(continuous variable),
(8) center (categorical variable).

Age at the first vaccine dose is calculated for each subject using his/her date of birth and his/her date of first dose (vaccination).

Age at the second vaccine dose is calculated for each subject using his/her date of birth and his/her date of second dose (vaccination).

The gender, the race, the height at Visit 1, the weight at Visit 1 and the center are recorded in the eCRF for each subject.

The BMI (Body Mass Index) is derived as follows: Weight (in kg) / Height² (in meters)

For a given subject and a given demographic variable, missing measurement will not be replaced. Therefore, analysis of demography will exclude subjects with missing measurements.

6.3.2. Efficacy

An episode of GE will be classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain is identified in a stool sample collected during the episode (see Table 12 for the allowed interval for stools collection). GE episode without stool sample/result available will not be considered in the analysis as a RV GE episode.

Table 12 Protocol defined interval for stools collected in case of gastroenteritis episode and tolerated deviation

Protocol defined range	Adapted range
Day 0 to Day 7 after onset of GE symptoms	Day 0 to the minimum of the following 2 timepoints 1) 7 days after the end of the GE episode 2) the day before onset of the next GE episode, if subject had several episodes of GE

RV GE for efficacy analysis is defined as an episode of GE in which rotavirus other than vaccine strain is identified in a stool sample collected during the episode.

Three efficacy follow-up periods will be considered:

- The first efficacy follow-up period starts from two weeks after Dose 2 of HRV vaccine or placebo and ends at Visit 5 (when subjects reached approximately one year of age).
- The second efficacy follow-up period starts on the day after the Visit 5 and ends at Visit 7 (when subjects reached approximately two year of age).
- The combined efficacy follow-up period starts from two weeks after Dose 2 of HRV vaccine or placebo and ends at Visit 7

In addition, for efficacy after Dose 1 based on the Total vaccinated cohort the follow-up period starts from Dose 1 of HRV vaccine or placebo and ends at Visit 5. Periods starting from Dose 1 up to 14 days post dose 2 and from dose 1 up to before dose 2 will also be considered.

To assess the intensity of RV GE using the 20-points Vesikari scale:

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting) are calculated by counting the number of days with presence (>0) of looser than normal stool (vomiting). Missing value at a specific day is considered as absence of looser than normal stool (vomiting) at that day.
- The maximum number of looser than normal stool (vomiting or fever) is defined as the maximum value observed from the number of looser than normal stool (vomiting or fever) recorded daily during the GE episode.
- As the treatment is recorded in the eCRF, score associated to the treatment can then be directly derived from the eCRF.
- Since the dehydration was not recorded in the eCRF, the following rule will be applied**:** a subject that had a GE episode is considered as being dehydrated between 1 to 5% if this subject received oral rehydration; a subject is considered as being dehydrated $\geq$ 6 % if the subject was hospitalized and/or received intravenous (IV) rehydration.

To assess the intensity of RV GE using the 24-points Clark scale:

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting, fever or behavioral symptoms) are calculated by counting the number of days with presence (>0) of looser than normal stool (vomiting, fever or behavioral symptoms). Missing value at a specific day is considered as absence of looser than normal stool (vomiting, fever or behavioral symptoms) at that day.
- The maximum number of looser than normal stool (vomiting or fever) is defined as the maximum value observed from the number of looser than normal stool (vomiting or fever) recorded daily during the GE episode.

The vaccine efficacy (VE) is defined as the percent reduction in the frequency of the relevant endpoint in vaccinated subjects compared with those subjects who received placebo. This is calculated as follows:

VE = vaccine efficacy = 1- RR = 1 – (ARV/ARU)

Where:

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 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.

RR = relative risk = ARV/ARU

95%CI on VE is calculated as detailed in annex 3.

6.3.3. Reactogenicity

The safety variables are classified as follow:

(1) solicited symptoms
(2) unsolicited adverse events (including SAEs and SAEs or AEs leading to drop-out)
(3) Concomitant vaccination
(4) Concomitant medication
(5) Exposure to HRV vaccine or Placebo
(6) Compliance in returning symptoms sheet

For a given dose, subjects with no symptoms (solicited or unsolicited) documented will be considered as subjects without symptoms (solicited or unsolicited).

6.3.4. Immunogenicity variables

The cut-off values of all antibodies are defined by the laboratory before the analysis and are described in Table 5 .

A seronegative subject is a subject whose concentration/titer is below the cut-off value.

A seropositive subject is a subject whose concentration/titer is greater than or equal to the cut-off value.

Seroprotection is defined as antibody concentration/titer greater than or equal to the seroprotection level

Seroconversion is defined as the appearance of antibodies (i.e. concentration/titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination

Immunogencity variables will be of two types:

- Binary variables: seropositivity/seroprotection/seroconversion rate at each sampling time point

- Continuous variables: individual antibody concentration or titer at each blood sampling time point,

The GMC (or GMT) calculations are performed by taking the anti-log of the mean of the log concentration (or titer) transformations. Antibody concentrations (or titers) below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC (or GMT) calculation.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis of immunogenicity excluded subjects with missing or non-evaluable measurements.

6.4. Group description

The following group description will be used for the efficacy, immunogenicity, demography, safety/reactogenicity and compliance analyses.

Study	Group order in tables	Group label in tables
444563/036	1	HRV
	2	Placebo

6.5. Interim analysis

Interim analysis on reactogenicity and immunogenicity data for a subset of subject in Czech Republic and Finland

An abridged study Report and Analysis Plan dated 27 June 2005 described analysis to be performed in the scope of an Interim analysis as planned per protocol. As quoted in the protocol,

"*In order to obtain early safety with relevance to other studies, an interim analysis on reactogenicity and immunogenicity will be performed on subjects from the Czech Republic and Finland only from the "immunogenicity and reactogenicity subset" with data available at Visit 3. This analysis will present a descriptive summary of reactogenicity data on solicited and unsolicited symptoms, immunogenicity for the study vaccine as well as immunogenicity data for childhood vaccines co-administered with each study vaccine dose. In order to ensure the study blinding is thoroughly maintained for the study sponsor, subjects family and investigators, the interim analysis will be performed by the independent data center supporting the IDMC. No study report will be written for the interim data. Access to the interim analysis results will be strictly controlled.*"

6.6. Demography/baseline characteristics

The following tables will be generated:

Table # in reference of annex 1	Abbreviated Title (see annex 1 for the proposed wording in the statistical report)	Total vacc cohort	Total vacc cohort (subset)	ATP reacto cohort (subset)	ATP immuno cohort (subset)	ATP efficacy year 1	ATP efficacy year 2
Table 13	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for efficacy with reasons for exclusion - Pooled countries	CR[P]					
Table 14	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for reactogenicity and from the ATP cohort for immunogenicity with reasons for exclusion - Pooled countries	CR[P]					
Table 15	Number of subjects at each visit and list of dropped-out subjects from Visits 1 to 5 – Pooled countries	WT[P]					
Table 15	Number of subjects at each visit and list of dropped-out subjects from Visits 1 to 7 – Pooled countries	WT[P]					
Table 16	Counts of subjects vaccinated, completed, dropped and reason for drop-out at visit 5 – Pooled countries	CR[P]					
Table 16	Counts of subjects vaccinated, completed, dropped and reason for drop-out at visit 7 – Pooled countries	CR[P]					
Table 17	Deviation from specification for age and intervals between study visits up to Visit 3	ST[C]					
Table 18	Minimum and maximum visit dates from visit 1 to visit 5 – Pooled countries	WT[P]					
Table 18	Minimum and maximum visit dates from visit 1 to visit 7 – Pooled countries	WT[P]					

Table 19	Number of days between the 2 doses of HRV/Placebo, and between Dose 2 of HRV/Placebo and Visit 3	ST[PC]				ST[PC]	
Table 20	Number of days between Dose 2 of HRV/Placebo and post-vaccination blood sampling at Visit 3		ST[PC]#		ST[PC]		
Table 21	Number of subjects enrolled in each country, by group	CR					
Table 22	Number of subjects enrolled at each centre, by group	ST[C]					
Table 23	Summary of demographic characteristics – For pooled countries or by country depending on the cohort	ST[PC]	ST[P]		ST[P]	CR[P]	CR[P]
Table 24	Demography for CTRS – Pooled countries	CTR[P]					
Table 25	Summary of feeding criteria at dose 1 and dose 2 of HRV vaccine or Placebo				ST[PC]	ST[PC]	
Table 26	Summary of epidemiological data	ST[PC]					
Table 27	Interval between the administration of childhood routine vaccination and the administration of the HRV/placebo vaccine – Pooled countries	WT[P]					
Table 28	Summary of co-administered vaccinations by dose	ST[C]	ST[C] Finland		ST[C]	ST[C]	
Table 29	Number of days between the second and the third dose of childhood routine vaccination, and between the third dose of childhood routine vaccination and the post-vaccination blood sampling at Visit X		ST[C]#		ST[C]		
Table 30	Summary of vaccinations other than HRV/placebo administered from birth until 30 days post Dose 2, excluding vaccination given on the day of HRV/placebo doses	ST[C]	ST[C] Finland				
Table 31	Number and percentage of subjects who received childhood routine vaccination dose(s) up to at least 21 days before blood sampling at visit X		ST[C]#		ST[C]		

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[P]=table generated for pooled countries
CTR = table for use in the clinical trial registration summary
#: a complementary analysis based on the total vaccinated cohort will be provided if more than 5% of the subjects are excluded from the ATP cohort for immunogenicity. The resulting tables will appear as supplemental tables.
CZ = Czech Republic, GE = Germany, FI = Finland, FR = France, IT = Italy, SP = Spain

6.7. Reactogenicity

The following tables will be generated:

		Total vacc cohort	**Total vacc cohort (subset)**	**ATP reacto cohort (subset)**
Table 32	Number and percentage of subjects who received HRV/placebo dose(s)	CR^{P} ST^{C}		
Table 33	Compliance in returning symptoms sheet		CR^{P} ST^{C}	ST^{P}#
Table 34	Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the solicited 8 days follow-up period		CR^{P}	ST^{P}#
Table 34	Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the solicited 8 days follow-up period		ST^{P}	ST^{P}#
Table 34	Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the solicited 8 days follow-up period		ST^{P}	ST^{P}#
Table 35	Percentage of subjects reporting each solicited general symptom included those grade 3 in intensity and those assessed as related to vaccination, during the solicited 8 days follow-up period, for each HRV/placebo dose		CR^{P} ST^{C} CTR^{P}	ST^{P}#
Table 36	Percentage of doses and of subjects reporting each solicited general symptom included those grade 3 in intensity and those assessed as related to vaccination, during the solicited 8 days follow-up period, for all HRV/placebo doses		ST^{PC} CTR^{P}	ST^{P}#
Table 35	Percentage of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the first 3-day (day 0, 1 or 2), for each HRV/placebo dose		WT^{PC}	
Table 36	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 first 3-day (day 0, 1 or 2), for all HRV/placebo doses		WT^{PC}	
Table 37	Statistical comparisons between groups for the percentage of subjects reporting each solicited symptom during the solicited 8 days follow-up period, after any HRV/placebo doses – Pooled countries		ST^{P}	
Table 38	Prevalence of diarrhea by day after Dose 1, during the solicited 8 days follow-up period – Pooled countries		ST^{P}	
Table 38	Prevalence of diarrhea by day after Dose 2, during the solicited 8 days follow-up period – Pooled countries		ST^{P}	
Table 38	Prevalence of vomiting by day after Dose 1, during the solicited 8 days follow-up period – Pooled countries		ST^{P}	
Table 38	Prevalence of vomiting by day after Dose 2, during the solicited 8 days		ST^{P}	

	follow-up period – Pooled countries			
Table 38	Prevalence of fever by day after Dose 1, during the solicited 8 days follow-up period – Pooled countries		ST[P]	
Table 38	Prevalence of fever by day after Dose 2, during the solicited 8 days follow-up period – Pooled countries		ST[P]	
Table 39	Percentage of subjects with missing values for diarrhea, by day, during the solicited 8 days follow-up period – Pooled countries		WT[P]	
Table 39	Percentage of subjects with missing values for vomiting, by day, during the solicited 8 days follow-up period – Pooled countries		WT[P]	
Table 39	Percentage of subjects with missing values for fever, by day, during the solicited 8 days follow-up period – Pooled countries		WT[P]	
Table 40	Duration (in days) of diarrhea, vomiting and fever during the solicited 8 days follow-up period – Pooled countries		WT[P]	
Table 41	Percentage of subjects with unsolicited symptoms classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 42	Percentage of subjects with unsolicited symptoms classified by MedDRA system organ class (SOC) and preferred term from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 43	Percentage of doses with unsolicited symptoms classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 44	Percentage of doses with unsolicited symptoms classified by MedDRA system organ class (SOC) and preferred term from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 41	Percentage of subjects with grade 3 unsolicited symptoms classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses – Pooled countries	CR[P]		
Table 42	Percentage of subjects with grade 3 unsolicited symptoms classified by MedDRA system organ class (SOC) and preferred term from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 43	Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 44	Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA system organ class (SOC) and preferred term from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 41	Percentage of subjects with unsolicited symptoms assessed as related to vaccination classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses – Pooled countries	CR[P]		
Table 42	Percentage of subjects with unsolicited symptoms assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred term from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		

Table 43	Percentage of doses with unsolicited symptoms assessed as related to vaccination classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 44	Percentage of doses with unsolicited symptoms assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred term from day 0 to day 30 after any HRV/placebo doses – Pooled countries	ST[P]		
Table 45	SAEs/AEs leading to drop-out from dose 1 of HRV/placebo up to visit 5, per group – Pooled countries	ST[P]		
Table 45	SAEs/AEs leading to drop-out after visit 5 up to visit 7, per group – Pooled countries	ST[P]		
Table 46	Percentage of subjects with SAEs occurring from Dose 1 of HRV/placebo up to Visit 5 – Pooled countries	CR[P]		
Table 46	Percentage of subjects with SAEs occurring from Dose 1 of HRV/placebo up to Visit 7 – Pooled countries	CR[P]		
Table 47	Number (%) of subjects with adverse events - Pooled countries	CTR[P]		
Table 48	Number (%) of subjects with serious adverse events from Dose 1 of HRV/placebo up to Visit 5 - Pooled countries	CTR[P]		
Table 48	Number (%) of subjects with serious adverse events from Dose 1 of HRV/placebo up to Visit 7 - Pooled countries	CTR[P]		
Table 49	Percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after HRV/placebo doses, by type	CR[P]		
Table 50	Percentage of doses and of subjects who took at least one concomitant medication during the study period, per type	WT[P]		

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[C]=table generated by country (CZ/GE/FI/FR/IT/SP)
[P]=table generated for pooled countries
CTR = table for use in the clinical trial registry summary
#= the analysis on the specified cohort will be presented as supplementary table in case it is performed to supplement the primary cohort. The analysis will be performed for pooled countries only.
CZ = Czech Republic, GE = Germany, FI = Finland, FR = France, IT = Italy, SP = Spain

6.7.1. Between groups assessment

All group comparisons with respect to reactogenicity will be exploratory.

Two-sided p-value from the Fisher exact test for the comparison between the HRV group and the placebo group will be computed for the following endpoints:

- For a given symptom, the percentage of subjects with solicited symptom of any intensity within 8 days after vaccination

- For a given symptom, the percentage of subjects with a grade "3" solicited symptom within 8 days after vaccination

- For a given symptom, the percentage of subjects with a solicited symptom assessed as related to vaccination within 8 days after vaccination

Two-sided asymptotic p-value – Farrington C.P. & Manning G., test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk (method3), statistics in Medicine, Vol 9, 1447-1451, 1990) and the standardized asymptotic 95% CIs for the differences between the HRV group and (minus) the Placebo group will be computed for the following endpoints:

- For unsolicited symptoms , unsolicited symptoms grade "3" in intensity and unsolicited symptoms assessed as related to the vaccination reported within 31 days after any vaccination , the percentage of subjects with a symptom within 31 days after any vaccination

- For SAEs

P-values less than 0.05 are used as an indicator of a possible difference between groups. However, since p-values are not adjusted for multiplicity of comparisons and did not account for clinical relevant differences, statistically significant findings should be interpreted with caution.

The following tables will be generated.

Table in reference of annex 1	**Denomination**
Table 37	For comparison on solicited symptoms
Tables 41, 42 and 46	For comparison on unsolicited symptoms and SAEs

6.8. Immunogenicity

The list of antigen that will be investigated is presented below:

Antigen	GMC or GMT?	Assay		Cut-off		Number of decimal digits		Tick marks on RCC's**	
		Method	Unit			GMC or GMT	GMC or GMT ratio	Low value	High value
anti-PRP	C	ELISA	µg/ml	0.15	1.0	3	2	0.01	1000
anti-SBA-MenC	T	Bactericidal assay	Dilution for 50% killing	1.8*	1:128	1	2	1	100000
anti-PSC	C	ELISA	µg/ml	0.30	2.0	2	2	0.1	1000
anti-Diphteria	C	ELISA	IU/ml.	0.1		3	2	0.01	100
anti-Tetanus	C	ELISA	IU/ml.	0.1		3	2	0.01	100
anti-PT	C	ELISA	EL.U/ml.	5		1	2	1	1000
anti-FHA	C	ELISA	EL.U/ml.	5		1	2	1	1000
anti-PRN	C	ELISA	EL.U/ml.	5		1	2	1	1000
anti-HBs	C	ELISA	MIU/ml.	10		1	2	1	100000
anti-Polio type 1	T	Micro-neutralisation test	Dilution for 50% neutralisation	8		1	2	1	100000
anti-Polio type 2	T	Micro-neutralisation test	Dilution for 50% neutralization	8		1	2	1	100000
anti-Polio type 3	T	Micro-neutralization test	Dilution for 50% neutralization	8		1	2	1	100000
anti-ROTA IgA	T	ELISA	IU/ml	20		1	2	10	100000
anti-4,6B,9V,14,18C,19F,23F Pneumococcal vaccine serotypes	C	ELISA	µg/ml	0.05	0.2	2	2	0.01	1000

* this limit corresponds to a seropositivity level
** all RCC's will use a log scale in base 10

6.8.1. Within groups assessment

The following tables will be generated:

Table in reference of annex 1	Denomination	Total vacc cohort (subset)	ATP immuno cohort (subset)
Table 51	Seroconversion rates and GMC for anti-rotavirus IgA antibodies		CR^{PC} CTR^{P}
Table 51	Seroconversion rates and GMC for anti-rotavirus IgA antibodies, by feeding criteria – Pooled countries		ST^{P}
Table 52	Seropositivity rates and GMC for anti-rotavirus IgA antibodies	ST^{PC}#	
Table 52	Seropositivity rates and GMC for anti-rotavirus IgA antibodies, by feeding criteria – Pooled countries	ST^{P}#	
Table 53	Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at visit 3		CR^{PC}
Table 53	Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at visit 3, by feeding criteria – Pooled countries		ST^{P}
Table 54	Anti-rotavirus IgA antibody GMC calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at visit 3	ST^{PC}#	
Table 54	Anti-rotavirus IgA antibody GMC calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at visit 3, by feeding criteria – Pooled countries	ST^{P}#	
Table 55	Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at visit 3 – Pooled countries		ST^{P}
Table 56	GMC and seropositivity/seroprotection rates for anti (each concomitant vaccine) antibody	ST^{C}#	CR^{C} CTR^{C}
Table 55	Reverse cumulative distribution curves for anti- (each concomitant vaccine) after the second dose of concomitant vaccine		ST^{C} (IT/FI/SP)
Table 55	Reverse cumulative distribution curves for anti- (each concomitant vaccine) after the third dose of concomitant vaccine		ST^{C}

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^{P}=table generated for pooled countries
CTR = table for use in the clinical trial registry summary
#: a complementary analysis based on the total vaccinated cohort will be provided if more than 5% of the subjects are excluded from the ATP cohort for immunogenicity. The resulting tables will appear as supplemental tables.
CZ = Czech Republic, GE = Germany, FI = Finland, FR = France, IT = Italy, SP = Spain

6.8.2. Between groups assessment

The following tables will be generated:

Table in reference of annex 1	Denomination	Total vacc cohort (subset)	ATP immuno cohort (subset)
Table 57	Difference in percentage of subjects who seroconverted for anti-rotavirus IgA antibody after Dose 2 between HRV and placebo groups – Pooled countries		ST[P]
Table 58	Difference in seropositivity/seroprotection rates one month after dose 2 of routine childhood vaccination between placebo and HRV groups, for the routine childhood vaccination		ST[C]
Table 58	Difference in seropositivity/seroprotection rates one month after dose 3 of routine childhood vaccination between placebo and HRV groups, for the routine childhood vaccination		ST[C]
Table 59	Ratio of GMT/Cs one month after dose 2 of routine childhood vaccination between placebo and HRV groups, for each routine childhood vaccine		ST[C]
Table 59	Ratio of GMT/Cs one month after dose 3 of routine childhood vaccination between placebo and HRV groups, for each routine childhood vaccine		ST[C]

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[C]=table generated by country (CZ/GE/FI/FR/IT/SP)
[P]=table generated for pooled countries
CZ = Czech Republic, GE = Germany, FI = Finland, FR = France, IT = Italy, SP = Spain

6.9. Analysis of efficacy

The following tables will be generated:

Table in reference of annex 1	Denomination	Total vacc cohort	ATP efficacy cohort
Table 60	Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 of HRV vaccine or placebo up to visit 5 – Pooled countries	$ST^{P\S}$	
Table 61	Percentage of subjects who reported GE episodes and RV GE episodes during each efficacy follow up period – Pooled countries	ST^{P}	CR^{P}
Table 62	Percentage of GE episodes with no available stool results during each efficacy follow-up period – Pooled countries	ST^{P}	ST^{P}
Table 63	Seasonal distribution of GE episode reported from 2 weeks after Dose 2 up to Visit 5		ST^{PC}
Table 63	Seasonal distribution of GE episode reported after Visit 5 up to Visit 7		ST^{PC}
Table 63	Seasonal distribution of RV GE episode reported from 2 weeks after Dose 2 up to Visit 5		ST^{PC}
Table 63	Seasonal distribution of RV GE episode reported after Visit 5 up to Visit 7		ST^{PC}
Table 64	Number of GE episodes and RV GE episodes reported during each efficacy follow-up period, by severity using the 20-point Vesikari scale – Pooled countries	ST^{P}	CR^{P}
Table 65	Number of GE episodes and RV GE episodes reported during each efficacy follow-up period, by severity using the 24-point Clark scale – Pooled countries	ST^{P}	ST^{P}
Table 66	Distribution of Vesikari score for RV GE episodes – Pooled countries	$ST^{P\S}$	ST^{P}
Table 66	Distribution of Clark score for RV GE episodes – Pooled countries	$ST^{P\S}$	ST^{P}
Table 67	Percentage of subjects with RV GE episodes reported during each efficacy follow-up period, by G serotype and P genotype – Pooled countries	ST^{P}	ST^{P}
Table 68	Number of RV GE episodes reported during each efficacy follow-up period, by G serotype and P genotype	ST^{PC}	CR^{PC}
Table 69	Characteristics (based on Vesikari scale) of RV GE episodes reported during each efficacy follow-up period, by main serotype (G1, non-G1,…) and overall – Pooled countries	$ST^{P\S}$	ST^{P}
Table 70	Characteristics (based on Clark scale) of RV GE episodes reported during each efficacy follow-up period, by main serotype (G1, non-G1,…) and overall – Pooled countries	$ST^{P\S}$	ST^{P}
Table 69	Characteristics of GE episodes reported during each efficacy follow-up period – Pooled countries	$ST^{P\S}$	ST^{P}
Table 71	Duration (in years) of each efficacy follow up period – Pooled countries	ST^{P}	ST^{P}
Table 72	Number of subjects vaccinated before the RV season		ST^{PC}

Table 73	Percentage of subjects reporting any RV GE episode and efficacy of the vaccine during each efficacy follow-up period	ST^{P} $ST^{C\S}$	CR^{P} ST^{C} CTR^{P}
Table 73	Percentage of subjects reporting any RV GE episode of G1 serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting any RV GE episode of non-G1 serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting any RV GE episode by main serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during each efficacy follow-up period	ST^{P} $ST^{C\S}$	CR^{P} ST^{C}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale) of G1 serotype and efficacy of the vaccine during each f efficacy ollow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale) of non-G1 serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale) by main serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects hospitalized due to RV GE episode and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting RV GE episode with medical attention and efficacy of the vaccine during each efficacy follow-up period	$ST^{PC\S}$	CR^{P} ST^{C}
Table 73	Percentage of subjects reporting any GE episode and efficacy of the vaccine during each efficacy follow-up period	$ST^{PC\S}$	ST^{PC}
Table 73	Percentage of subjects reporting severe GE episode (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during each efficacy follow-up period	$ST^{PC\S}$	ST^{PC}
Table 73	Percentage of subjects hospitalized due to GE episode and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	ST^{P}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=16 in using the 24-point Clark scale) and efficacy of the vaccine during each efficacy follow-up period	ST^{P} $ST^{C\S}$	CR^{P} ST^{C}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=16 in using the 24-point Clark scale) of G1 serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=16 in using the 24-point Clark scale) of non-G1 serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=16 in using the 24-point Clark scale) by main serotype and efficacy of the vaccine during each efficacy follow-up period	$ST^{P\S}$	CR^{P}
Table 73	Percentage of subjects reporting any RV GE episode and efficacy of the		ST^{P}

	vaccine during each efficacy follow-up period, by feeding criteria		
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during each efficacy follow-up period, by feeding criteria		ST[P]
Table 73	Percentage of subjects reporting any RV GE episode and efficacy of the vaccine during each efficacy follow-up period, by serological status for IgA antibody concentration at Visit 3		ST[P]
Table 73	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during each efficacy follow-up period, by serological status for IgA antibody concentration at Visit 3		ST[P]
Table 74	Percentage of subjects reporting RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 – pooled countries		ST[P]
Table 74	Percentage of subjects reporting RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 – pooled countries		ST[P]
Table 75	Efficacy of the vaccine against RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 2 up to Visit 4 – pooled countries		ST[P]
Table 75	Efficacy of the vaccine against RV GE episodes with a score ≥X on the Clark scale from 2 weeks after Dose 2 up to Visit 4 – pooled countries		ST[P]
Table 76	Percentage of subjects in the HRV vaccine group reporting RV GE during the first efficacy follow-up period and on combined efficacy periods, by status of anti-rotavirus IgA antibody concentration at Visit 3 – Pooled countries		ST[P]
Table 77	Efficacy of the vaccine against any RV GE during the first efficacy follow-up period, by Cox – Pooled countries		WT[P]
Table 77	Efficacy of the vaccine against any RV GE of G1 serotype during the first efficacy follow-up period, by Cox – Pooled countries		WT[P]
Table 77	Efficacy of the vaccine against any RV GE of non-G1 serotype during the first efficacy follow-up period, by Cox – Pooled countries		WT[P]
Table 78	The Kaplan Meier curve for any RV GE / any RV GE due to G1 serotype / any RV GE due to non-G1 serotypes during the first efficacy follow-up period – Pooled countries		WT[P]

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[C]=table generated by country (CZ/GE/FI/FR/IT/SP)
[P]=table generated for pooled countries
[§] = This table will only be produced for the analysis from dose 1 up to visit 5
All table defined in the column "Total vacc cohort" will be generated for the analysis from dose 1 up to visit 5, from dose 1 up to 14 post dose 2 and from dose 1 up to before dose 2 on the total vaccinated cohort, except when '[§]' is mentioned

7. CHANGE FROM PROTOCOL

In case of significant non-compliance with study procedures for reporting solicited symptoms, additional analyses (i.e. more than 5% of doses not documented by a symptom sheet for at least each group) will be made excluding all doses for which no data on solicited symptoms are available.

The following planned analyses will not be perfromed as almost all subjects were vaccinated during the RV epidemic season :

- To assess vaccine efficacy against any and severe RV GE during the first efficacy follow-up period in subjects who completed the two-dose vaccination course before the RV epidemic season *versus* those who were vaccinated during the RV epidemic season.

8. INDIVIDUAL LISTINGS

8.1. Demography

There are 12 individual data listings linked to the demography analysis, they are sorted by country, centre and group (with the candidate vaccine first) and then by subject number and each subject centre are indicated. The parameter "Elig." (for Eligibility) indicates if a subject has been eliminated from the ATP cohort of reactogenicity, immunogenicity and efficacy-first and second follow-up (code E), from the ATP cohort of immunogenicity (code I), from the ATP cohort of immunogenicity and efficacy-first and second follow-up (code J), from the ATP cohort of immunogenicity and efficacy-second follow-up (code K), from the ATP cohort of efficacy-first and second follow-up (code F) or from the ATP cohort of efficacy-second follow-up (code G).

- Appendix Table I.A - Elimination codes: gives for each subject the elimination code(s) he/she has been assigned if applicable.
- Appendix Table I.B - Demography: indicates for each subject, his/her age, gender and race, height, weight;
- Appendix Table I.Ci - Dates of birth, vaccination, blood sampling and visits: lists for each subject, his/her date of birth, consent date, vaccination date(s), blood sampling date(s) and visit date(s);
- Appendix Table I.Cii – Reason for visit not done
- Appendix Table I.D - General medical history - Physical examination: lists for each subject of the diagnosis, signs and symptoms if any, reported during the physical examination preceding the vaccination(s);
- Appendix Table I.Ei –Study conclusion at Visit 5: indicate for each subject if he/she completed the study or not, and if not, the reason for non-completion and whether this reason is linked to an Adverse event (AE); the last contact date and whether the subject was in good condition at this last contact;
- Appendix Table I.Eii- Study conclusion at Visit 7: indicates for each subject, if the blinding code was broken or not and if yes the reason why; if he/she completed the

study or not, and if not, the reason for non-completion and whether this reason is linked to an Adverse event (AE); the last contact date and whether the subject was in good condition at this last contact;

- Appendix Table I.Eiii – Subject for whom the code has been broken: indicates for each subject, if the blinding code was broken or not and if yes the reason why
- Appendix Table I.I - Reason for non-administration of vaccine
- Appendix Table I.J - Reason for non-Eligibility
- Appendix Table I.K – Feedings characteristics at visit 1, visit 2
- Appendix Table I.L - Epidemiological data: number of siblings, attendance to day care center

8.2. Safety/ Reactogenicity

There are 8 individual data listings related to the safety analysis, they are sorted by country, centre and group (with the candidate vaccine first) and then by subject number and each subject centre are indicated. The parameter: Elig. (for Eligibility) indicates if a subject has been eliminated from the ATP cohort of reactogenicity, immunogenicity and efficacy-first and second follow-up (code E), from the ATP cohort of immunogenicity (code I), from the ATP cohort of immunogenicity and efficacy-first and second follow-up (code J), from the ATP cohort of immunogenicity and efficacy-second follow-up (code K), from the ATP cohort of efficacy-first and second follow-up (code F) or from the ATP cohort of efficacy-second follow-up (code G).

- Appendix Table II.B.i - Solicited general adverse events (Fever, Cough/Runny nose, Irritability/Fussiness, Loss of appetite, Vomiting): for each subject, it indicates whether the subject has experienced a solicited general symptom and, if yes, whether he/she has experienced each of the solicited general symptoms. For each specific general symptom experienced, the relationship coding and the outcome coding are indicated, along with the intensity coding for each follow-up day. For fever the temperature recorded for each follow-up day is indicated, for vomiting the number of vomiting cases recorded for each follow-up day is indicated.
- Appendix Table II.B.ii - Solicited general adverse events (Diarrhea): for each subject, it indicates whether the subject has experienced diarrhea. If diarrhea was experienced, the relationship coding and the outcome coding are indicated, along with the number of diarrhea coding and behavioral symptoms (Irritability/less playful, Lethargic, Listless, Seizure) for each follow-up day.
- Appendix Table II.Ci. - Unsolicited adverse events within 31 days post vaccination: each of them are listed with the verbatim, the corresponding keyword, the corresponding MedDRA preferred term and its code, the corresponding MedDRA body system and its code, the related vaccine dose, the start date, the day of onset, the end date, the duration (in days), the coding of intensity and the outcome. Whether it is a serious adverse event and if yes the corresponding CIOMs number are indicated.
- Appendix Table II.Cii. - Unsolicited adverse events started more than 31 days post vaccination.
- Appendix Table II.Ciii. – Serious adverse events reported from Visit 1 up to Visit 5.
- Appendix Table II.Civ. – Serious adverse events reported from Visit 1 up to Visit 7.

- Appendix Table II.D.i-Concomitant medication: each of them are listed with the related (or previous) vaccine dose, the relative day of onset, the start date, the end date, the duration (days), the generic name, a code (P: prophylactic) and the medical indication.
- Appendix Table II.D.ii - Intercurrent vaccination: each of them are listed by Trade name and with the start date.

8.3. Immunogenicity

There are 2 individual data listings related to the immunogenicity analysis, they are sorted by country, centre and group (with the candidate vaccine first) and then by subject number and each subject centre are indicated. The parameter: Elig**.** (for Eligibility) indicates if a subject has been eliminated from the ATP cohort of reactogenicity, immunogenicity and efficacy-first and second follow-up (code E), from the ATP cohort of immunogenicity (code I), from the ATP cohort of immunogenicity and efficacy-first and second follow-up (code J), from the ATP cohort of immunogenicity and efficacy-second follow-up (code K), from the ATP cohort of efficacy-first and second follow-up (code F) or from the ATP cohort of efficacy-second follow-up (code G).

- Appendix Table III.A: Immunogenicity: gives for each subject who had blood sample(s) taken, the concentration reached for each antibody tested.

- Appendix Table III.B: Results of the samples collected in case of intussusception: gives for each subject who reported an IS the results of the samples collected.

8.4. Efficacy

There are 2 individual data listings related to the efficacy analysis, they are sorted by country, centre and group (with the candidate vaccine first) and then by subject number and each subject centre are indicated. The parameter: Elig. (for Eligibility) indicates if a subject has been from the ATP cohort of reactogenicity, immunogenicity and efficacy-first and second follow-up (code E), from the ATP cohort of immunogenicity (code I), from the ATP cohort of immunogenicity and efficacy-first and second follow-up (code J), from the ATP cohort of immunogenicity and efficacy-second follow-up (code K), from the ATP cohort of efficacy-first and second follow-up (code F) or from the ATP cohort of efficacy-second follow-up (code G).

- Appendix Table V.A: Detailed information of gastroenteritis episodes: gives for each subject who reported a GE episode, the related vaccine dose, the day of onset, the treatment given, the treatment type, the medical attention given, the date of the symptoms, the number of looser than normal stools per day, the number of vomiting episode per day, the temperature per day, the stools collection date, presence of behavioral symptoms (irritability/less playful, lethargic, listless, seizure).
- Appendix Table V.B: gastroenteritis stool collection results : gives the stools result for each subject who reported a GE episode and with stool samples collected

9. ANNEX 1: TEMPLATE OF TABLES

All the tables and figures used to support the final analysis (up to the end of the first efficacy follow-up period) and the annex analysis (up to the end of the second efficacy follow-up period) of demographic characteristics, safety/reactogenicity, immunogenicity and efficacy are described below with their content and their skeleton.

Tables will be generated by group.

In each of the tables, the following order will be used:

- HRV
- Placebo

9.1. Study cohort, Analysis of demographics and Description of Vaccine administration

9.1.1. Study Cohorts

9.1.1.1. Number of subjects and cohorts definition

The number and the percentage of subjects included in the Total enrolled cohort, the Total vaccinated cohort, the Total vaccinated cohort for the immunogenicity and reactogenicity subset, the ATP cohort for reactogenicity, the ATP cohort for immunogenicity and the ATP cohort for efficacy are presented in a table such as Table 13 and Table 14. Reasons for elimination from these ATP cohorts are also detailed in these tables.

These tables will be provided for pooled countries.

Table 13 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for efficacy with reasons for exclusion - Pooled countries

Title	Total	Percent	HRV	Placebo
Total enrolled cohort	**xxx**		**xxx**	**xxx**
Study vaccine dose not administrated at all but subject number allocated (code 1030)	x (x)		x (x)	x (x)
Total vaccinated cohort	**xxx**	**100**	**xxx**	**xxx**
Administration of intercurrent vaccine(s) forbidden in the protocol (code 1040)	x (x)		x (x)	x (x)
Randomisation failure (code 1050)	x (x)		x (x)	x (x)
Randomisation code broken (code 1060)	x (x)		x (x)	x (x)
Study vaccine dose not administered according to protocol (code 1070)	x (x)		x (x)	x (x)
At least one study vaccine dose not administered (code 3010)	x (x)		x (x)	x (x)
Subjects not entered into the surveillance period of the first efficacy follow-up period (code 3020)	x (x)		x (x)	x (x)
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response (code 3030)	x (x)		x (x)	x (x)
ATP cohort for efficacy - first efficacy follow-up period and combined efficacy follow-up periods	**xxx**	**xx.x**	**xxx**	**xxx**
Subjects not entered into the surveillance period of the second efficacy follow-up period (code 4020)	x (x)		x (x)	x (x)
ATP cohort for efficacy - second efficacy follow-up period	**xxx**	**xx.x**	**xxx**	**xxx**

Source: Appendix Table IA

Notes:

Percent = percentage of subjects in the considered ATP cohort relative to the total vaccinated cohort

Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:

n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number

s = number of subjects with the elimination code assigned.

The ATP cohort for analysis of efficacy during the first efficacy follow-up period and on combined efficacy period include all vaccinated subjects with no elimination codes beginning with one thousand or three thousand with the exception of code 1035.

The ATP cohort for analysis of efficacy during the second efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one thousand or three thousand or four thousand with the exception of code 1035.

Table 14 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for reactogenicity and from the ATP cohort for immunogenicity with reasons for exclusion - Pooled countries

Title	Total	Percent	HRV	Placebo
Total enrolled cohort	**xxx**		**xxx**	**xxx**
Study vaccine dose not administrated at all but subject number allocated (code 1030)	x (x)		x (x)	x (x)
Total vaccinated cohort	**xxx**	**100**	**xxx**	**xxx**
Subject for whom solicited symptoms were not to be collected and who were not planned to be bled for all blood sampling visits (code 1035)	x (x)		x (x)	x (x)
Total vaccinated cohort for the immunogenicity and reactogenicity subset	**xxx**	**xx.x**	**xxx**	**xxx**
Administration of intercurrent vaccine(s) forbidden in the protocol (code 1040)	x (x)		x (x)	x (x)
Randomisation failure (code 1050)	x (x)		x (x)	x (x)
Randomisation code broken (code 1060)	x (x)		x (x)	x (x)
Study vaccine dose not administered according to protocol (code 1070)	x (x)		x (x)	x (x)
Initially positive or unknown status for rotavirus on the day of dose 1 (code 1500)	x (x)		x (x)	x (x)
ATP cohort for reactogenicity	**xxx**	**xx.x**	**xxx**	**xxx**
Protocol violation (inclusion/exclusion criteria) (code 2010)	x (x)		x (x)	x (x)
Administration of any medication forbidden by the protocol (code 2040)	x (x)		x (x)	x (x)
Underlying medical condition forbidden by the protocol (code 2050)	x (x)		x (x)	x (x)
Concomitant infection by rotavirus other than vaccine strain which may influence immune response (code 2060)	x (x)		x (x)	x (x)
Non compliance with vaccination schedule (including wrong and unknown dates) or subject with incomplete vaccination schedule but with serological data at visit 3(code 2080)	x (x)		x (x)	x (x)
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	x (x)		x (x)	x (x)
Essential serological data missing (code 2100)	x (x)		x (x)	x (x)

Title	Total	Percent	HRV	Placebo
ATP cohort for immunogenicity	**xxx**	**xx.x**	**xxx**	**xxx**

Source: Appendix Table IA
Notes:
Percent = percentage of subjects in the considered ATP cohort relative to the total vaccinated cohort
Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned.
The ATP cohort for reactogenicity includes all vaccinated subjects with no elimination codes beginning with one thousand.
The ATP cohort for immunogenicity includes all vaccinated subjects with no elimination codes beginning with one or two thousand.

9.1.1.2. Number of subjects at each visit and list of dropped-out subjects

The number of subjects who have dropped out (along with their identification numbers) and the number of subjects who attended each visit are described in a table such as Table 15. From an analysis perspective, a "drop-out" is any subject who did not return for the concluding visit foreseen in the protocol. A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study even if all study procedures (e.g. blood sampling, vaccination) were not performed.

These analyses will be provided for pooled countries for the total vaccinated cohort.

Table 15 Number of subjects at each visit and list of dropped- out subjects from Visit 1 to 5(7) – Pooled countries - Total vaccinated cohort

	VIS1 VC1	Pid	VIS2 VC2	Pid	VIS3 BS2	PID	VIS4	…
Number of subjects								
Dropped out subject number								

Notes:
VC = time point of vaccination
BS = time point of blood sampling
VIS = visit

Subject	Reasons for drop-out

9.1.1.3. Number of dropped-out subjects and reasons for drop-out

Reasons for drop-out are summarized in a table such as Table 16. The "number of subjects completed" is the number of subjects who completed the last study visit. The "number of subjects dropped-out" is the number of subjects who did not return for the last study visit.

These analyses will be generated for pooled countries for the total vaccinated cohort.

Table 16 Counts of subjects vaccinated, completed, dropped, and reason for drop-out at Visit 5(7) - Pooled countries - Total vaccinated cohort

	Group		
	HRV	Placebo	Total
Number of subjects enrolled and vaccinated			
Number of subjects who completed Visit 5(7)			
Number of subjects dropped out at Visit 5(7)			
Reasons for drop-out :			
Serious Adverse Event			
Non-serious adverse event			
Protocol violation§			
Consent withdrawal (not due to an adverse event)			
Migrated/moved from study area			
Lost to follow-up (subjects with incomplete vaccination course)			
Lost to follow-up (subjects with complete vaccination course)			
Others*			

Source: Appendix Table IE
Notes:
Enrolled and vaccinated = number of subjects who where enrolled in the study and received at least one dose
Completed = number of subjects who completed study Visit 5/7
Dropped-out = number of subjects who did not return for study Visit 5/7
§Protocol violation:
*Other :

9.1.1.4. Deviations from specifications for age and intervals between study visits

The age range and the intervals between visits defined in the protocol should be followed as closely as possible. However, if circumstances dictate other intervals (adapted intervals), this does not necessarily lead to the exclusion of the subject(s) from analysis. This means that the subjects for which visit intervals are within the adapted intervals are not excluded from the ATP cohort for immunogenicity, but those for which visit intervals are outside these adapted intervals are excluded.

The number and percentage of subjects out of these defined and adapted limits for age and/or intervals between visits up to Visit 3 are described in a table such as Table 17.
The denominator used to calculate the percentage is for:
- AGE: the number of vaccinated subjects

- Dose 1 – Dose 2: the number of subjects having received Dose 1 and Dose 2 of study vaccine
- Dose 2 – Visit 3: the number of subjects having received Dose 2 and present at visit 3

These tables will be provided by country (Czech Republic, Germany, Finland, France; Italy and Spain) for the Total vaccinated cohort. Please refer to Table 3 for a description of interval between study visits.

Table 17 Deviations from specifications for age and intervals between study visits up to Visit 3 – Czech Republic (Germany; Finland; France; Italy; Spain) - Total vaccinated cohort

Group	Age at Dose 1	Dose 1 – Dose 2		Dose 2 – Visit 3	
	Protocol	Protocol	Adapted	Protocol	Adapted
	from 6 to 14 weeks	from xx to xx days	from xx to xx days	from xx to xx days	from xx to xx days
HRV	n = x subjects (from -x to y Weeks) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)
Placebo	n = x subjects (from -x to y Weeks) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)	n = x subjects (from -x to y Days) x.x% of xxx (x subjects with empty value)

Source: Appendix Table IC
Notes:
n = number of subjects out of the specified range of age or out of the considered interval
from xx to xx Days/Weeks = from the minimum to the maximum interval in Days or in Weeks, for the subjects out of the considered range
% (for age) = proportion of subjects out of the specified interval using as denominator the number of subjects in the considered cohort.
% (for dose 1-dose 2 , for dose 2- Visit 3) = proportion of subjects out of the specified interval among subjects present at the considered visits.

An additional table such as Table 18 provides, for each visit, the earliest and latest date among all subjects. This table will be generated for pooled countries on the total vaccinated cohort.

Table 18 Minimum and maximum visit dates from visit 1 to visit 5 (7) – Pooled countries - Total vaccinated cohort

Visit number	Activity number	Earliest date	Latest date
1	10	DDMMMYYYY	DDMMMYYYY
2	20	DDMMMYYYY	DDMMMYYYY
3	30	DDMMMYYYY	DDMMMYYYY
4	40	DDMMMYYYY	DDMMMYYYY
5	50	DDMMMYYYY	DDMMMYYYY

The intervals between the 2 doses of HRV/Placebo and between Dose 2 and Visit 3 will also be summarized as defined below for each country (Czech Republic, Germany, Finland, France, Italy or Spain) and pooled countries, on the Total vaccinated cohort and on the ATP cohort for efficacy (**only interval between the 2 doses of HRV/Placebo**) .

Table 19 Number of days between the 2 doses of HRV/Placebo, and between Dose 2 of HRV/Placebo and Visit 3 - Pooled countries (Czech Republic; Germany; Finland; France; Italy; Spain) - Total vaccinated cohort (ATP cohort for efficacy)

	HRV	Placebo	Total
Number of days between Dose 1 and Dose 2			
Parameters	**Value**	**Value**	**Value**
N	XXX		
Mean	XX.x		
SD	XX.xx		
Minimum	XX		
Q1	XX.x		
Median	XX.x		
Q3	XX.x		
Maximum	XX		
Number of days between Dose 2 of HRV/Placebo and Visit 3			
Parameters	**Value**	**Value**	**Value**
N			
Mean			
SD			
Minimum			
Q1			
Median			
Q3			
Maximum			

Source: Appendix Table IC
Notes:
N for number of days between Dose 1 and Dose 2: N= Number of subjects with two doses administered
N for number of days between Dose 2 of HRV/Placebo and Visit 3: N = Number of subjects with dose 2 administered and Visit 3 done
Q1 = 25th percentile
Q3 = 75th percentile
SD = standard deviation

The interval between Dose 2 and the post-vaccination blood sampling at Visit 3 will also be summarized as defined below for each country (Czech Republic, Germany, Finland, France, Italy or Spain) and pooled countries, on the ATP cohort for immunogenicity and on the Total vaccinated cohort for the reactogenicity and immunogenicity subset (if analysis of immunogenicity on the total vaccinated cohort need to be performed (refer to section 6.2)).

Table 20 Number of days between Dose 2 of HRV/Placebo and post-vaccination blood sampling at Visit 3 - Pooled countries (Czech Republic; Germany; Finland; France; Italy; Spain) - ATP cohort for immunogenicity (Total vaccinated cohort for the reactogenicity and immunogenicity subset , if applicable)

	HRV	Placebo	Total
Number of days between Dose 2 of HRV/Placebo and post-vaccination blood sampling at Visit 3			
Parameters	**Value**	**Value**	**Value**
N **Mean** **SD** **Minimum** **Q1** **Median** **Q3** **Maximum**			

Source: Appendix Table IC
Notes:
N = Number of subjects with dose 2 administered and with anti-Rotavirus IgA result at post-vaccination blood sampling at visit 3
Q1 = 25th percentile
Q3 = 75th percentile
SD = standard deviation

9.1.1.5. Number of subjects by country and per centre

The number and percentage of subjects enrolled by group and by country are tabulated such as in Table 21.

The number and percentage of subjects enrolled by group and by center are also tabulated such as in Table 22. This table will be provided by country (Czech Republic, Germany, Finland, France, Italy, and Spain).

These analyses will be performed on the total vaccinated cohort

Table 21 Number of subjects enrolled in each country by group - Total vaccinated cohort

	HRV	Placebo	Total	
Country	**n**	**n**	**n**	**%**
Czech Republic	XXX	XXX	XXX	XX.x
Germany				
Finland				
France				
Italy				
Spain				

Source: Appendix table I.B
Notes:
n = number of subjects enrolled in each group or in total for a given country or for all countries.

% = percentage of subjects enrolled in each group for a given country or for all countries.
All countries = sum of all subjects in each group or in total for all groups.

Table 22 Number of subjects enrolled at each centre by group - Czech Republic (Germany; Finland; France; Italy; Spain) - Total vaccinated cohort

	HRV	Placebo	Total	
Center	n	n	n	%
[redacted]	XXX	XXX	XXX	XX.x

Source: Appendix table I.B
Notes:
n = number of subjects enrolled in each group or in total for a given centre or for all centres.
% = percentage of subjects enrolled in each group or in total for a given centre or for all centres.
All = sum of all subjects in each group or in total for all groups
Centre = GSK assigned centre number

9.1.2. Demography

9.1.2.1. Summary of demographic characteristics

A general table such as Table 23 presents the main demographic characteristics (age at the first and second dose, weight and height descriptive statistics, gender and racial distribution). This table will be generated for pooled countries on the Total vaccinated cohort, on the Total vaccinated cohort for the reactogenicity and immunogenicity subset, on the ATP cohort for efficacy and on the ATP cohort for immunogenicity.

The same table will also be generated for each country (Czech Republic, Germany, Finland, France, Italy, and Spain) on the Total vaccinated cohort.

Table 23 Summary of demographic characteristics - Pooled countries (Czech Republic; Germany; Finland; France; Italy; Spain) - Total vaccinated cohort (Total vaccinated cohort for the reactogenicity and immunogenicity subset; ATP cohort for efficacy; ATP cohort for immunogenicity)

		HRV N = xxx		Placebo N = xxx		Total N = xxx	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at the first dose (weeks)	**Mean**						
	SD						
	Minimum						
	Q1						
	Median						
	Q3 **Maximum**						
Age at the second dose (weeks)	**Mean**						
	SD						
	Minimum						
	Q1						
	Median						
	Q3						
	Maximum						
	Unknown						
Gender	**Female**						
	Male						
Race	**Black**						
	White/Caucasian						
	Arabic/North African						
	East/South East Asian						
	South Asian						
	American Hispanic						
	Japanese						
	Other						
Height (cm) at the first dose	**Mean**						
	SD						
	Median						
	Unknown						
Weight (kg) at the first dose	**Mean**						
	SD						
	Median						
BMI (kg/m²) at the first dose	**Mean**						
	SD						
	Median						
	Unknown						

Source: Appendix Table I.B
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
Q1 = 25th percentile
Q3 = 75th percentile

SD= standard deviation
BMI = body mass index [Weight (in kg) /Height² (in meters)]

The following Table will be generated for CTR (Clinical Trial Registration), for pooled countries on the Total vaccinated cohort.

Table 24 Demography for CTRS - Pooled countries - Total vaccinated cohort

Number of subjects	**HRV**	**PLACEBO**
Planned, N		
Randomised, N (Total Vaccinated Cohort)		
Completed, n (%)		
Total Number Subjects Withdrawn, n (%)		
Withdrawn due to Adverse Events, n (%)		
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)		
Demographics	**HRV**	**PLACEBO**
N (Total Vaccinated Cohort)		
Females:Males		
Mean Age, months (SD)		
White/caucasian, n (%)		

Table 25 summarize the feeding criteria. This table will be generated for each country (Czech Republic, Germany, Finland, France, Italy, and Spain) and for pooled countries on the the ATP cohort for efficacy and on the ATP cohort for immunogenicity.

Table 25 Summary of feeding criteria at dose 1 and dose 2 of HRV vaccine or Placebo, by country and for pooled countries - ATP cohort for efficacy (ATP cohort for immunogenicity)

		HRV N =		**Placebo N =**		**Total N = 3994**	
COUNTRY	**Infant was breast feeded at**	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	**Both dose**					237	79.3
	One dose					17	5.7
	None					45	15.1
Finland	**Both dose**					1994	69.0
	One dose					357	12.4
	None					539	18.7
France	**Both dose**					46	31.5
	One dose					27	18.5
	None					73	50.0
Germany	**Both dose**					158	54.7
	One dose					45	15.6

		HRV N =		Placebo N =		Total N = 3994	
COUNTRY	**Infant was breast feeded at**	**n**	**%**	**n**	**%**	**n**	**%**
	None					86	29.8
Italy	**Both dose**					14	56.0
	One dose					3	12.0
	None					8	32.0
Spain	**Both dose**					156	45.2
	One dose					75	21.7
	None					114	33.0
Overall total	**Both dose**					2605	65.2
	One dose					524	13.1
	None					865	21.7

Source: Appendix I.K
Notes:
N= total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category

9.1.3. Epidemiological data

The number of siblings per subject and the attendance to day care centre will be summarized such as in Table 26, by country and for pooled country on the total vaccinated cohort

Table 26 Summary of epidemiological data - Pooled countries (Czech Republic; Germany; Finland; France; Italy; Spain) - Total vaccinated cohort

		HRV N = XXX		Placebo N = XXX		Total N = XXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Number of siblings	**0** **1** **2** **…**	XXX XXX XXX XXX	XX.x XX.x XX.x XX.x				
Attendance to day care center at visit 1	**Yes** **No**						
Attendance to day care center at visit 2	**Yes** **No**						
Attendance to day care center at visit 3	**Yes** **No**						
Attendance to day care center at visit 4	**Yes** **No**						
Attendance to day care center at visit 5	**Yes** **No**						
Attendance to day care center at visit 6	**Yes** **No**						

		HRV N = XXX		Placebo N = XXX		Total N = XXX	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Attendance to day care center at visit 7	**Yes** **No**						

Source: Appendix I.L
Notes:
N= total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category

9.1.4. Childhood routine vaccination

In the following tables, a subject will be considered to have received childhood routine vaccination at a specified time-point if he or she received Infanrix Hexa at this time-point for Czech Republic, Finland or Italy, or if she or he received one of the routine combinations vaccines defined in section 4 at this time-point for France, Germany and Spain.

9.1.4.1. Co-administration with the HRV or Placebo vaccine

The number of subjects for whom routine childhood vaccinations have not been administered on the same day as Dose 1 or Dose 2 of HRV vaccine or placebo will be tabulated per group as presented in Table 27.

This Table will be generated for pooled countries on the Total vaccinated cohort.

Table 27 Interval between the administration of childhood routine vaccination and the administration the HRV/placebo vaccine – Pooled countries - Total vaccinated cohort

	VAC1- RCV 1	VAC2- RCV 2
Group	**Protocol interval: from 0 to 0 D**	**Protocol interval: from 0 to 0 D**
HRV	n=X subjects (from XX to XX D) XX% of XX	n=X subjects (from XX to XX D) XX% of XX
Placebo	n=X subjects (from XX to XX D) XX% of XX	n=X subjects (from XX to XX D) XX% of XX

Source: Appendix Table IC
Notes:
VAC1: visit for first dose of HRV vaccine or Placebo
VAC2: visit for second dose of HRV vaccine or Placebo
RCV1: date for first dose of routine childhood vaccination
RCV 2: date for second dose of routine childhood vaccination
n=x subjects = number of subjects for whom routine childhood vaccination was not administered on the same day as HRV/Placebo vaccine
from xx to xx D = from the minimum to the maximum interval in Days, for the subjects for whom routine childhood vaccination was not administered on the same day as HRV/Placebo vaccine

% = : proportion of subjects for whom of routine childhood vaccination was not administered on the same day as HRV/Placebo vaccine among subjects who have received a dose of HRV/placebo and of routine childhood vaccination for the same schedule time point

Summary of vaccinations co-administered on the day of Dose 1 or Dose 2 of HRV/Placebo vaccine will be summarized as in Table 28.

This table will be generated for each country (Czech Republic, Germany, Finland, France, Italy, and Spain) on the Total vaccinated cohort, and also on the Total vaccinated cohort for reactogenicity and immunogenicity subset for Finland.

The same table will be generated by country (Czech Republic, Germany, Finland, France, Italy, Spain) on the ATP cohort for efficacy and on the ATP cohort for immunogenicity.

Table 28 Summary of co-administered vaccinations by dose - Czech Republic (Germany; Finland; France; Italy; Spain) - Total vaccinated cohort (Total vaccinated cohort for the reactogenicity and immunogenicity subset (Finland); ATP cohort for efficacy; ATP cohort for immunogenicity)

Dose 1		
Category	***Each group*** **N=**	
	n	**%**
Any **Infanrix Hexa** **Prevenar** **Meningitec** **Flu** **BCG** **Other**		
Dose 2		
Category	***Each group*** **N=**	
	n	**%**
Any **Infanrix Hexa** **Prevenar** **Meningitec** **Flu** **BCG** **Other**		

Source: Appendix Table II.Dii
Notes:
N = total number of subjects having received the considered dose of HRV/placebo
n/% = number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

9.1.4.2. Administration of the third dose of Childhood Routine Vaccination

The intervals between the second and the third dose of childhood routine vaccination and between the third dose of childhood routine vaccination and the post-vaccination blood

sampling at Visit X* will be summarized per group and overall as defined below for Czech Republic, Finland, France, Germany, Italy and Spain. This analysis will be performed on the ATP cohort for immunogenicity and on the Total vaccinated cohort for reactogenicity and immunogenicity subset (if analysis of immunogenicity on the total vaccinated cohort need to be performed (refer to section 6.2)).

Visit X* = Visit 4: for Spain
= Visit 6: for Finland and Italy
= Visit 3: for Czech Republic, France and Germany

Table 29 Number of days between the second and the third dose of childhood routine vaccination, and between the third dose of childhood routine vaccination and the post-vaccination blood sampling at Visit X - Czech Republic (Germany; Finland; France; Italy; Spain) - ATP cohort for immunogenicity (Total vaccinated cohort for reactogenicity and immunogenicity subset, if applicable)

	HRV	Placebo	Total
Number of days between the second dose and the third dose of childhood routine vaccination			
Parameters	**Value**	**Value**	**Value**
N	XXX		
Mean	XX.x		
SD	XX.xx		
Minimum	XX		
Q1	XX.x		
Median	XX.x		
Q3	XX.x		
Maximum	XX		
Number of days between the third dose of childhood routine vaccination and the post-vaccination blood sampling at Visit X			
Parameters	**Value**	**Value**	**Value**
N			
Mean			
SD			
Minimum			
Q1			
Median			
Q3			
Maximum			

Source: Appendix Table II.Dii

Notes:

N for Number of days between the second the third dose of childhood routine vaccination: N = Number of subjects who have been administered the second and the third dose of childhood routine vaccination

N for Number of days between the third dose of childhood routine vaccination and the post-vaccination blood sampling at Visit X: N = Number of subjects who have been administered the third dose of childhood routine vaccination before blood sampling at Visit X and with result at post-vaccination blood sampling at Visit X

Q1 = 25th percentile

Q3 = 75th percentile

SD = standard deviation

9.1.4.3. Intercurrent vaccination

Intercurrent vaccination administered from birth until 30 days post Dose 2, excluding vaccination given on the day of HRV/placebo doses will be summarized per groups as in Table 30 for each country (Czech Republic, Germany, Finland, France, Italy, and Spain), on the Total vaccinated cohort.

The same table will be generated for Finland on the total vaccinated cohort for reactogenicity and immunogenicity subset.

Table 30 Summary of vaccinations other than HRV/placebo administered from birth until 30 days post Dose 2, excluding vaccination given on the day of HRV/placebo doses - Czech Republic (Germany; Finland; France; Italy; Spain) - Total vaccinated cohort (Total vaccinated cohort for the reactogenicity and immunogenicity subset in Finland)

Before Dose 1			
Category	***Each group*** **N=**		
	n*	**n**	**%**
Any			
Infanrix Hexa			
Prevenar			
Meningitec			
Flu			
BCG			
Other			
Between Dose 1 and Dose 2§			
Category	***Each group*** **N=**		
	n*	**n**	**%**
Any			
Infanrix Hexa			
Prevenar			
Meningitec			
Flu			
BCG			
Other			
Between Dose 2 and 30 days post Dose 2			
Category	***Each group*** **N=**		
	n*	**n**	**%**
Any			
Infanrix Hexa			
Prevenar			
Meningitec			
Flu			
BCG			

Other			

Source: Appendix Table II.Dii
Notes:
N = Before visit 1 and between Dose 1 and Dose 2 : total number of subjects having received dose 1of HRV/placebo
Between Dose 2 and 30 days post Dose 2: total number of subjects having received Dose 2 of HRV/placebo
n*= number of doses administered of the specified vaccination
Any n* = total number of doses of vaccinations administered other than HRV/placebo and excluding vaccination given on the day of HRV/placebo dose
n/% = number/percentage of subjects who received at least one specified vaccination between the considered visits excluding vaccination given on the day of HRV/placebo doses
§= up to last contact of conclusion at Visit 5 if dose 2 of HRV/placebo was not administered

A global overview of the number of childhood routine vaccination received from Visit 1 up to 21 days before each blood sampling time point will be summarized per group, as in Table 31 for each country (Czech Republic, Germany, Finland, France, Italy, Spain) on the ATP cohort for immunogenicity and on the Total vaccinated cohort for reactogenicity and immunogenicity subset (if analysis of immunogenicity on the total vaccinated cohort need to be performed (refer to section 6.2).

Table 31 Number and percentage of subjects who received childhood routine vaccination dose(s) from Visit 1 up to 21 days before blood sampling at visit X - Czech Republic (Germany; Finland; France; Italy; Spain) - ATP cohort for immunogenicity (Total vaccinated cohort for the reactogenicity and immunogenicity subset, if applicable)

	Each group N =	
Total number of doses of Infanrix Hexa received from Visit 1 up 21 days before the post-vaccination blood sampling planned at Visit 3 (4 or 6) *(For any country*)	**n**	**%**
1 **2** **3**		
Any		
Total number of doses of MenC received from Visit 1 up to 21 days before the post-vaccination blood sampling planned at Visit *4 (For Spain only)*	**n**	**%**
1 **2** **3**		
Any		
Total number of doses of Prevenar received from Visit 1 up to 21 days before the post-vaccination blood sampling planned at Visit 3/6 *(For Germany or France)*	**n**	**%**
1 **2** **3**		
Any		

Source: Appendix Table II.Dii
Notes:
N = number of subjects included in each group with result at post-vaccination blood sampling at Visit 3/4/6
n/% = number/percentage of subjects receiving the specified total number of doses of the specified routine vaccination
Any = number and percentage of subjects receiving at least one dose of the specified routine vaccination

9.2. Analysis of Reactogenicity/Safety

As an introduction to the reactogenicity/safety analysis, a global overview of the number of vaccine doses received in each group and overall are tabulated as in Table 32. This analysis will be generated separately for Czech Republic, Germany, Finland, France, Italy, Spain and for pooled countries on the Total vaccinated cohort.

Table 32 Number and percentage of subjects who received HRV/placebo dose(s) - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - Total vaccinated cohort

Total number Of doses received	HRV (N = XXX)		Placebo (N = XXX)		Total (N = XXX)	
	n	%	n	%	n	%
0	XXX	XX.x				
1						
2						
Any						

Source: Appendix Table I.C.
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

The number of doses administered, the number of symptom sheets (SS) transcribed for general symptoms and the compliance for general symptoms will also be tabulated in a table such as Table 33. The compliance in returning symptom sheets will be tabulated separately for Czech Republic, Germany, Finland, France, Italy, Spain and for pooled countries on the Total vaccinated cohort for reactogenicity and immunogenicity subset and on the ATP cohort for reactogenicity (if analysis of reactogenicity on the ATP cohort need to be performed (refer to section 6.2)).

Compliance % is defined as the number of general symptom sheets completed divided by the number of doses administered for a specified vaccination (dose) and group.

Table 33 Compliance in returning symptom sheets - Czech Republic (Germany; Finland; France; Italy; Spain; Pooled countries) - Total vaccinated cohort for reactogenicity and immunogenicity subset (ATP cohort for reactogenicity, if applicable)

Dose	Group	Number of doses	Number of general SS	Compliance % general SS
1	**HRV Placebo**	XXX	XXX	XX.x
2	**HRV Placebo**			
Total	**HRV Placebo**			

Source: Appendix table I.C
Notes:
SS = Symptom sheets used for the collection of general solicited symptoms
Compliance % = (number of doses with symptom sheet return / number of administered HRV/placebo doses) X 100

9.2.1. All symptoms

The percentage (with exact 95 % Confidence Interval [CI]) of doses followed by any solicited or unsolicited symptoms during the solicited 8 day follow-up period after vaccination are tabulated per dose and overall and by group as in Table 34. For the overall doses analysis, the 95% CI computation assumes independence between doses.

The percentage (with exact 95 % CI) of subjects with any solicited or unsolicited symptoms are also tabulated per group in the same table.

Two similar tables are drawn for grade 3 symptoms (solicited or unsolicited) and for symptoms (solicited or unsolicited) with relationship assessed as related to the vaccine.

These analyses will be generated for pooled countries on the total vaccinated cohort for reactogenicity and immunogenicity subset and on the ATP cohort for reactogenicity (if analysis of reactogenicity on the ATP cohort need to be performed (refer to section 6.2)).

Table 34 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the solicited 8 days follow-up period - Pooled countries - Total vaccinated cohort for reactogenicity and immunogenicity subset (ATP cohort for reactogenicity, if applicable)

		Symptoms				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV Placebo	xxx	xxx	xx.x	xx.x	xx.x
Dose 2	HRV Placebo					
Overall/dose	HRV Placebo					
Overall/subject	HRV Placebo					

Source: Appendix table II.B and II.C
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/% = 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, LL = Lower Limit, UL = Upper Limit

9.2.2. Solicited general symptoms

9.2.2.1. Each solicited general symptoms

The percentage of doses (with exact 95 % CI) reporting each individual solicited general symptom, symptoms assessed as related to the vaccine and symptoms grade 3 in intensity, for the whole solicited follow-up period (day 0 - day 7), are tabulated for each group, after each dose in a table such as Table 35.

An overall dose analysis and the percentage (with exact 95 % CI) of subjects reporting each of the individual solicited general symptoms will also be tabulated as in Table 36. For this overall dose analysis, the 95% CI computation assumes independence between doses.

The analyses presented in Table 35 and Table 36 will be generated separately for Czech Republic, Germany, Finland, France, Italy, Spain and for pooled countries, on the total vaccinated cohort for reactogenicity and immunogenicity subset and on the ATP cohort for reactogenicity (if analysis of reactogenicity on the ATP cohort need to be performed (refer to section 6.2)).

Similar tables, such as Table 35 and Table 36 will also be generated for the first 3-days of the solicited follow-up period (day 0 - day 2) on the total vaccinated cohort for reactogenicity and immunogenicity subset.

Table 35 Percentage of subjects reporting each solicited general symptom included those graded "3" in intensity and those assessed as related to vaccination, during the solicited 8 days follow-up period, for each HRV/placebo dose - Czech Republic (Germany; Finland; France; Italy; Spain; Pooled countries) - Total vaccinated cohort for reactogenicity and immunogenicity subset (ATP cohort for reactogenicity, if applicable)

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough / runny nose	Total Grade 3 Related	XXX	XXX	XX.x	XX.x	XX.x	XXX	XXX	XX.x	XX.x	XX.x
Diarrhea	Total Grade 3 Related										
Fever	Total Grade 3 Related										
Irritability / Fussiness	Total Grade 3 Related										
Loss of appetite	Total Grade 3 Related										
Vomiting	Total Grade 3 Related										
Dose 2											
Cough / runny nose	Total Grade 3 Related										
Diarrhea	Total Grade 3 Related										
Fever	Total Grade 3 Related										
Irritability / Fussiness	Total Grade 3 Related										
Loss of appetite	Total Grade 3 Related										
Vomiting	Total Grade 3 Related										

Source: Appendix table II.B
Notes:
N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for the considered dose
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

Table 36 Percentage of doses and of subjects reporting each solicited general symptoms included those grade 3 in intensity and those assessed as related to vaccination, during the solicited 8 days follow-up period, for all HRV/placebo doses - Czech Republic (Germany; Finland; France; Italy; Spain; Pooled countries) - Total vaccinated cohort for reactogenicity and immunogenicity subset (ATP cohort for reactogenicity, if applicable)

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose											
Cough / runny nose	Total Grade 3 Related	XXX	XXX	XX.x	XX.x	XX.x	XXX	XXX	XX.x	XX.x	XX.x
Diarrhea	Total Grade 3 Related										
Fever	Total Grade 3 Related										
Irritability / Fussiness	Total Grade 3 Related										
Loss of appetite	Total Grade 3 Related										
Vomiting	Total Grade 3 Related										
Overall/subject											
Cough / runny nose	Total Grade 3 Related										
Diarrhea	Total Grade 3 Related										
Fever	Total Grade 3 Related										
Irritability / Fussiness	Total Grade 3 Related										
Loss of appetite	Total Grade 3 Related										

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Vomiting	**Total** **Grade 3** **Related**										

Source: Appendix table II.B
Notes:
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, LL = Lower Limit, UL = Upper Limit

Statistical comparison will be tabulated such as in Table 37 for subjects reporting each of the individual solicited general symptoms. This analysis will be performed for pooled countries on the Total vaccinated cohort for reactogenicity and immunogenicity subset.

The analyses of reactogenicity and safety planned numerous group comparisons through p-value computation. The p-values will be used as an aid to explore potential difference worth further attention (significance level of alpha=0.05) and care must be taken when interpreting putative statistically significant findings since there was no multiplicity adjustment, and the rate of false signals may be considerable large due to the number of comparisons.

Table 37 Statistical comparisons between groups for the percentage of subjects reporting each solicited symptom during the solicited 8 days follow-up period, after any HRV/placebo doses - Pooled countries - Total vaccinated cohort for reactogenicity and immunogenicity subset

		Pooled countries
Overall/subject		
		HRV versus Placebo
Symptoms	**Type**	**P-value**
Cough / runny nose	**Total** **Grade 3** **Related**	X.xxx
Diarrhea	**Total** **Grade 3** **Related**	
Fever	**Total** **Grade 3** **Related**	
Irritability / Fussiness	**Total** **Grade 3** **Related**	
Loss of appetite	**Total** **Grade 3** **Related**	

		Pooled countries
Overall/subject		
		HRV versus Placebo
Symptoms	**Type**	**P-value**
Vomiting	**Total** **Grade 3** **Related**	

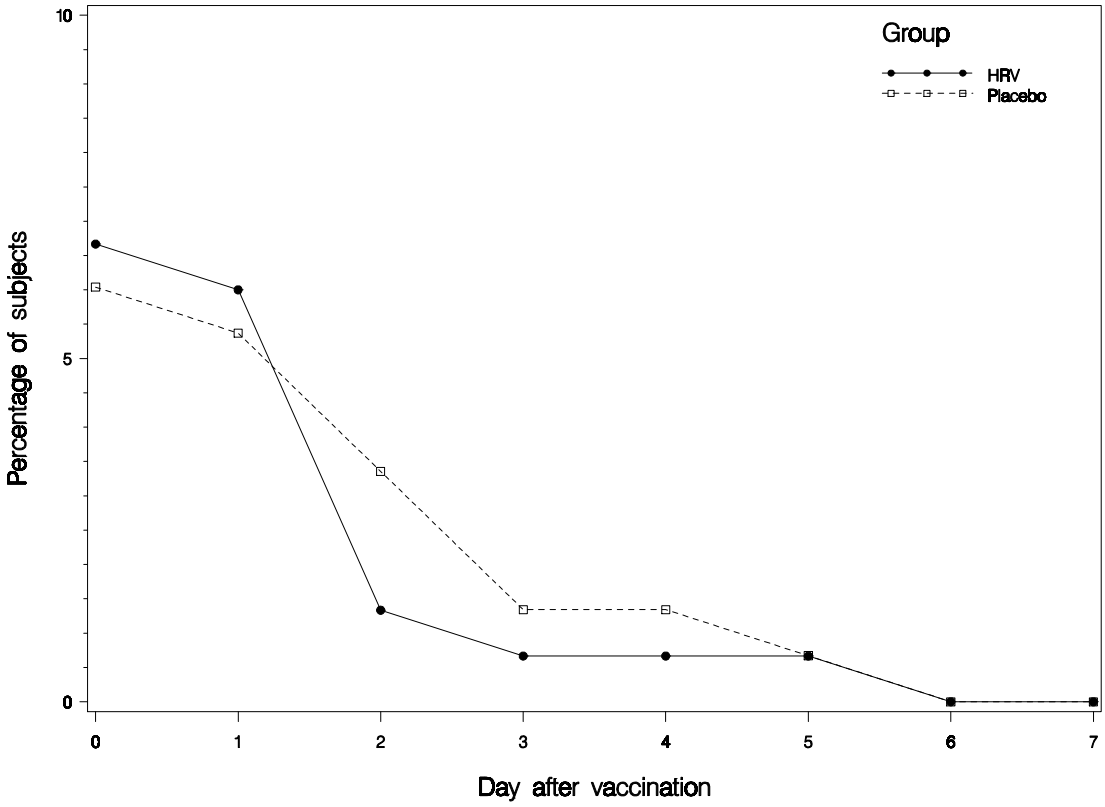
Source: Appendix table II.B
Notes:
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
P-value = results of comparison of percentage of subjects reporting the specified solicited symptom after any doses between groups by two-sided Fisher's exact test (significant level of alpha = 0.05)

In addition, descriptive comparison between groups of the diarrhea, vomiting and fever prevalence by day during the solicited follow-up period are described graphically as in Table 38. Prevalence is the percentage of subjects who reported the event at a certain (fixed) time point among doses administered.

Note that subjects with missing diarrhea (vomiting/fever) value on a specific day are considered as subject without diarrhea (vomiting/fever) on that day (i.e. no imputation rule or modification of the denominator is done). Table 39 presents the number of missing values.

Analysis presented in Table 38 and in Table 39 will be presented for pooled countries on the Total vaccinated cohort for the reactogenicity and immunogenicity subset.

Table 38 Prevalence of diarrhea (vomiting; fever) by day after Dose 1 (Dose 2), during the solicited 8 days follow-up period – Pooled countries - Total vaccinated cohort for reactogenicity and immunogenicity subset



Source: Appendix II.B
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Table 39 Percentage of subjects with missing values for diarrhea (vomiting, fever) by day, during the solicited 8 days follow-up period - Pooled countries - Total vaccinated cohort for reactogenicity and immunogenicity subset

	(Each dose) ***(Each group)*** **N**	
	n	**%**
Day 0 … **Day 7**		

N= number of subjects reporting diarrhea (vomiting, fever)
n/%= number/percentage of subjects with missing values, by day

Finally, the number of days (not necessarily consecutive days) with diarrhea, vomiting and fever respectively, during the solicited follow-up period (day 0 – day 7) by dose and for overall doses are summarized in a table such as Table 40. Missing value at a specific day is considered as absence of the symptom on that day.

This analysis will be presented for pooled countries on the Total vaccinated cohort for reactogenicity and immunogenicity subset.

Table 40 Duration* (in days) of diarrhea, vomiting and fever during the solicited 8 days follow-up period – Pooled countries - Total vaccinated cohort for the reactogenicity and immunogenicity subset

Solicited symptom	Dose	Group	n	Mean	Min	Q1	Median	Q3	Max
Fever	Dose 1	HRV Placebo	XX	X.x	X.x	X.x	X.x	X.x	X.x
	Dose 2	HRV Placebo							
	Overall/Dose	HRV Placebo							
Vomiting	Dose 1	HRV Placebo							
	Dose 2	HRV Placebo							
	Overall/Dose	HRV Placebo							
Diarrhea	Dose 1	HRV Placebo							
	Dose 2	HRV Placebo							
	Overall/Dose	HRV Placebo							

Source: Appendix II.B

Notes: n = number of doses reporting the specified solicited symptom with value for at least one day of follow-up
Q1 = 25th percentile
Q3 = 75th percentile
Duration* = number of days, not necessarily consecutive days, with presence of the symptoms. Missing value at a specific day is considered as absence of the symptom on that day

9.2.3. Unsolicited symptoms

Unsolicited symptoms occurring within 31 days (day 0 - day 30) after each dose will be summarized according to the MedDRA dictionary Preferred terms and/or SOC terms.

Each unsolicited symptom is associated to the last HRV vaccine or placebo dose administered before the symptom. The onset day is defined as the number of days between that dose and the start date of the unsolicited symptom.

Unsolicited symptoms will be investigated in terms of percentage of subjects (such as in Table 41 and Table 42) and of doses (such as in Table 43 and Table 44) reporting symptoms during the unsolicited follow-up period after any dose.

- the percentage of subjects reporting a specified unsolicited symptom after any dose during the unsolicited follow-up period is calculated, considering as denominator the number of subjects having received at least one study dose
- the percentage of doses reporting a specified unsolicited symptom after any dose is defined as the percentage of doses administered reporting this specified symptom during the unsolicited follow-up period, among all study doses administered.

These analyses will be generated for pooled countries on the Total vaccinated cohort.

Similar tables will be generated for grade 3 and for symptoms assessed as related to vaccination.

Table 41 Percentage of subjects with unsolicited symptoms classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

Primary System Organ Class (CODE)	HRV					Placebo					Risk Difference (HRV minus Placebo)			P-Value
	N	n	%	95% CI*		N	n	%	95% CI*		Value	95 % CI**		
				LL	UL				LL	UL		L.L	U.L	
At least one symptom *(each SOC)*														

Source: Appendix II.Ci
Notes:
N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified symptom reported within 31 days after any HRV/placebo dose
At least one symptom = number of subjects reporting at least one unsolicited adverse event within 31 days after any HRV/placebo dose, whatever the MedDRA SOC
95% CI* = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI** = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified symptom within 31 days after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account).

Table 42 Percentage of subjects with unsolicited symptoms classified by MedDRA system organ class (SOC) and Preferred term (PT) from day 0 to day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

Primary System Organ Class (CODE)	Preferred term (CODE)	HRV					Placebo					Risk Difference (HRV minus Placebo)			P-Value
		N	n	%	95% CI*		N	n	%	95% CI*		Value	95 % CI**		
					LL	UL				LL	UL		L.L	U.L	
At least one symptom (each SOC)	(each Preferred term)														

Source: Appendix II.Ci
Notes:
N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified symptom reported within 31 days after any HRV/placebo dose
At least one symptom = number of subjects reporting at least one unsolicited adverse event within 31 days after any HRV/placebo dose, whatever the MedDRA PT
95% CI* = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI** = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified symptom within 31 days after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account).

Table 43 Percentage of doses with unsolicited symptoms classified by MedDRA system organ class (SOC) from day 0 to day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

Primary System Organ Class (CODE)	HRV					Placebo				
	D	d	%	95% CI*		D	d	%	95% CI*	
				LL	UL				LL	UL
At least one symptom *(each SOC)*										

Source: Appendix II.Ci
Notes:
D=Total number of doses administered
d/%= number/percentage of doses followed by at least one report of the specified symptom within 31 days after any HRV/placebo dose
At least one symptom = number of dose with report of at least one unsolicited adverse event within 31 days after any HRV/placebo dose, whatever the MedDRA SOC
95% CI* = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI** = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of dose reporting the specified symptom within 31 days after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must

be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account).

Table 44 Percentage of doses with unsolicited symptoms classified by MedDRA system organ class (SOC) and Preferred term (PT) from day 0 to day 30 after any HRV/placebo doses - Pooled countries - Total vaccinated cohort

Primary System Organ Class (CODE)	Preferred term (CODE)	HRV					Placebo				
		D	d	%	95% CI*		D	d	%	95% CI*	
					LL	UL				LL	UL
At least one symptom (each SOC)	(each Preferred term)										

Source: Appendix II.Ci
Notes:
D=Total number of doses administered
d/%= number/percentage of doses followed by at least one report of the specified symptom within 31 days after any HRV/placebo dose
At least one symptom = number of dose with report of at least one unsolicited adverse event within 31 days after any HRV/placebo dose, whatever the MedDRA PT
95% CI* = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI** = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of dose reporting the specified symptom within 31 days after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account).

SAEs/AEs leading to drop-out will be listed as in Table 45. This analysis will be performed for pooled countries on the Total vaccinated cohort .

Table 45 SAEs/AEs leading to drop-out from dose 1 of HRV/placebo up to visit 5 (after visit 5 up to visit 7), per group – Pooled countries - Total vaccinated cohort

Country	Subject number	Symptom (verbatim)	MedDRA Preferred term	SAE/AE	Timing (dose/day)	Relationship to vaccination	Outcome
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.							

The number of subjects with SAEs occurring between Dose 1 of HRV/placebo and visit 5 (7) will also be summarized as in Table 46. This analyse will be performed for pooled countries on the Total vaccinated cohort.

Table 46 Percentage of subjects with SAEs occurring from Dose 1 of HRV/placebo up to Visit 5 (7) - Pooled countries - Total vaccinated cohort

	HRV					Placebo					Risk Difference (HRV minus Placebo)			
				95% CI*					95% CI*			95% CI**		
Category	N	n	%	LL	UL	N	n	%	LL	UL	%	LL	UL	P-Value
At least one SAE	XX	XX	XX.x	XX.x	XX.x	XX	XX	XX.x	XX.x	XX.x	XX.xx	XX.xx	XX.xx	X.xxx
At least one IS	XX	XX	XX.x	XX.x	XX.x	XX	XX	XX.x	XX.x	XX.x	XX.xx	XX.xx	XX.xx	X.xxx

Source: Appendix II.Ci
Notes:
N = total number of subjects having received dose 1 of HRV/placebo
n/%= number/percentage of subjects reporting at least once the specified SAE
95% CI* = exact 95% confidence interval, LL = lower limit, UL = upper limit
95% CI** = asymptotic standardised 95% confidence interval; LL = lower limit, UL = upper limit
P-value = results of comparison of percentage of subjects reporting the specified SAE after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Tables 47 and 48 will be generated for CTR (Clinical Trial Registration), for pooled countries on the Total vaccinated cohort.

Table 47 Number (%) of subjects with adverse events - Pooled countries - Total vaccinated cohort

Most frequent adverse events - On-Therapy (occuring within day 0-30 following vaccination)	HRV N = 172	PLACEBO N = 86
Subjects with any AE(s), n(%)	172 (100.0)	86 (100.0)
Rhinitis	59 (34.3)	26 (30.2)
Nervousness	48 (27.9)	22 (25.6)
Fever	30 (17.4)	8 (9.3)
upper resp tract infection	22 (12.8)	11 (12.8)
Conjunctivitis	17 (9.9)	15 (17.4)
Coughing	20 (11.6)	8 (9.3)
otitis media	18 (10.5)	6 (7.0)
Gastroesophageal reflux	18 (10.5)	4 (4.7)
Flatulence	16 (9.3)	4 (4.7)
Fatigue	11 (6.4)	5 (5.8)

Most frequent adverse events - On-Therapy (occuring within day 0-30 following vaccination)	**HRV N = 172**	**PLACEBO N = 86**
abdominal pain	11 (6.4)	3 (3.5)
crying abnormal	6 (3.5)	5 (5.8)
tooth ache	4 (2.3)	5 (5.8)

Table 48 Number (%) of subjects with serious adverse events from Dose 1 of HRV/placebo up to Visit 5 (7) - Pooled countries - Total vaccinated cohort

All SAEs	**HRV N = 205**	**PLACEBO N = 99**
Subjects with any SAE(s), n(%) [n related]	15 (7.3) [0]	4 (4.0) [0]
Appetite increased	1 (0.5) [0]	0 (0.0) [0]
Asthma	1 (0.5) [0]	0 (0.0) [0]
Bronchitis	3 (1.5) [0]	1 (1.0) [0]
Crying abnormal	1 (0.5) [0]	0 (0.0) [0]
Eczema	1 (0.5) [0]	0 (0.0) [0]
Fever	1 (0.5) [0]	0 (0.0) [0]
Gastroenteritis	1 (0.5) [0]	0 (0.0) [0]
infection bacterial	1 (0.5) [0]	0 (0.0) [0]
infection viral	1 (0.5) [0]	0 (0.0) [0]
Injury	1 (0.5) [0]	0 (0.0) [0]
Laryngitis	0 (0.0) [0]	1 (1.0) [0]
Meningitis	0 (0.0) [0]	1 (1.0) [0]
otitis media	2 (1.0) [0]	0 (0.0) [0]
Pneumonia	4 (2.0) [0]	0 (0.0) [0]
Seborrhea	0 (0.0) [0]	1 (1.0) [0]
Somnolence	1 (0.5) [0]	0 (0.0) [0]
upper resp tract infection	1 (0.5) [0]	1 (1.0) [0]
All fatal SAEs	**HRV N = 265**	**PLACEBO N = 133**
Subjects with any SAE(s), n(%) [n related]	0 (0.0) [0]	0 (0.0) [0]

9.2.4. Concomitant medications and vaccinations

9.2.4.1. Number and percentage of subjects who took at least one concomitant medication

The number and percentage of subjects who used medication concomitantly during the solicited follow-up period (Day 0 – Day 7) are tabulated as in Table 49. These analyses will be generated on the Total vaccinated cohort for pooled countries.

The following levels will be considered:

- Any medication
- Any antipyretics
- Prophylactic antipyretics
- Any antibiotics

The percentages are calculated using, as denominator, the number of subjects who received the considered dose.

Antipyretics and antibiotics are defined by applying the WHO drug dictionary to the medication collected in the eCRF.

Table 49 Percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after HRV/placebo doses, by type - Pooled countries - Total vaccinated cohort

Type of medication	***(Each dose)***			
	(Each group) N =			
	n	**%**	**95% CI**	
			L.L.	**UL**
Any medication Any antipyretics Prophylactic antipyretics Any antibiotics				

Source: Appendix Table II.D.1
Notes:
N = number of subjects having received the considered dose
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from day 0 to day 7 after vaccination
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

The same analyses will be generated for the whole study period:

Table 50 Percentage of doses and of subjects who took at least one concomitant medication during the study period, by type - Pooled countries - Total vaccinated cohort

Type of medication	***(Each dose)***			
	(Each group) N =			
	n	**%**	**95% CI**	
			L.L.	**UL**
Any medication Any antipyretics Prophylactic antipyretics Any antibiotics				

Source: Appendix Table II.D.1
Notes:

N = number of subjects having received the considered dose
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once after the considered dose during the study period
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

9.3. Immunogenicity

The ATP analysis includes all tables described in Section 9.3. For the total analysis, some of these tables are added as Supplements if the percentage of subjects excluded from the ATP immunogenicity cohort exceeds 5 %.

9.3.1. Within group assessement

9.3.1.1. Summary of anti-rotavirus IgA antibody concentrations

GMCs (Geometric Mean antibody Concentrations) and seroconversion rates are calculated for each group, at each time point that blood sample is available. These descriptive statistics are tabulated with their 95% CI in a table such as Table 51 for the ATP cohort for immunogenicity.

Table 52 is a lay-out of the same analysis in case an analysis on the total vaccinated cohort for reactogenicity and immunogenicity subset is performed (Seropositivity rates are considered instead of Seroconversion rate in this case).

GMCs (expressed in U/ml) are computed by giving an arbitrary value of half the cut-off for non-detectable concentrations. The 95% CI limits for GMCs are calculated by taking the antilog of the 95% confidence interval limits of the mean $\log_{10}$ antibody concentration. These latter limits are calculated under the assumption of normal distribution of the $\log_{10}$ antibody concentration but unknown variance (see Annex 3: section 11.2).

These analysis will be generated per group, per country and for pooled countries. Tables 51 and 52 will also be generated by feeding criteria for pooled counties (breast fed at one dose at least, breast fed at none of the doses).

Table 51 Seroconversion rates and GMCs for anti-Rotavirus IgA antibodies - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - ATP cohort for immunogenicity

				≥ 20 U/ml				GMC		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
(Each Country)	HRV	PRE PII(M3-M4)								
	Placebo	PRE PII(M3-M4)								
Pooled Country	HRV	PRE PII(M3-M4)								
	Placebo	PRE PII(M3-M4)								

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(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)

Table 52 Seropositivity rates and GMCs for anti-Rotavirus IgA - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

				≥ 20 U/ml				GMC		
						95% CI			95% CI	
Country	Group	Timing	N	n	%	LL	UL	value	LL	UL
(Each Country)	HRV	PRE PII(M3-M4)								
	Placebo	PRE PII(M3-M4)								
Pooled Country	HRV	PRE PII(M3-M4)								
	Placebo	PRE PII(M3-M4)								

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(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)

Table 53 presents anti-rotavirus IgA GMCs calculated on subjects who seroconverted for anti-rotavirus IgA at Visit 3.

Table 54 is a lay-out of the same analysis in case an analysis on the total vaccinated cohort for reactogenicity and immunogenicity subset is applicable (Seropositivity rates are considered instead of Seroconversion rate in this case).

These analysis will be generated per group, per country and for pooled countries. Tables 52 and 53 will also be generated by feeding criteria for pooled countries (breast fed at one dose at least, breast fed at none of the doses).

Table 53 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at visit 3 - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - ATP cohort for immunogenicity

				GMC		
					95% CI	
Country	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
(Each country)	**HRV**	**PII(M3-M4)**				
	Placebo	**PII(M3-M4)**				
Pooled countries	**HRV**	**PII(M3-M4)**				
	Placebo	**PII(M3-M4)**				

Notes:
N = number of subjects who seroconverted for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)

Table 54 Anti-rotavirus IgA antibody GMC calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at visit 3 - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - Total vaccinated cohort for the reactogenicity and immunogenicity subset

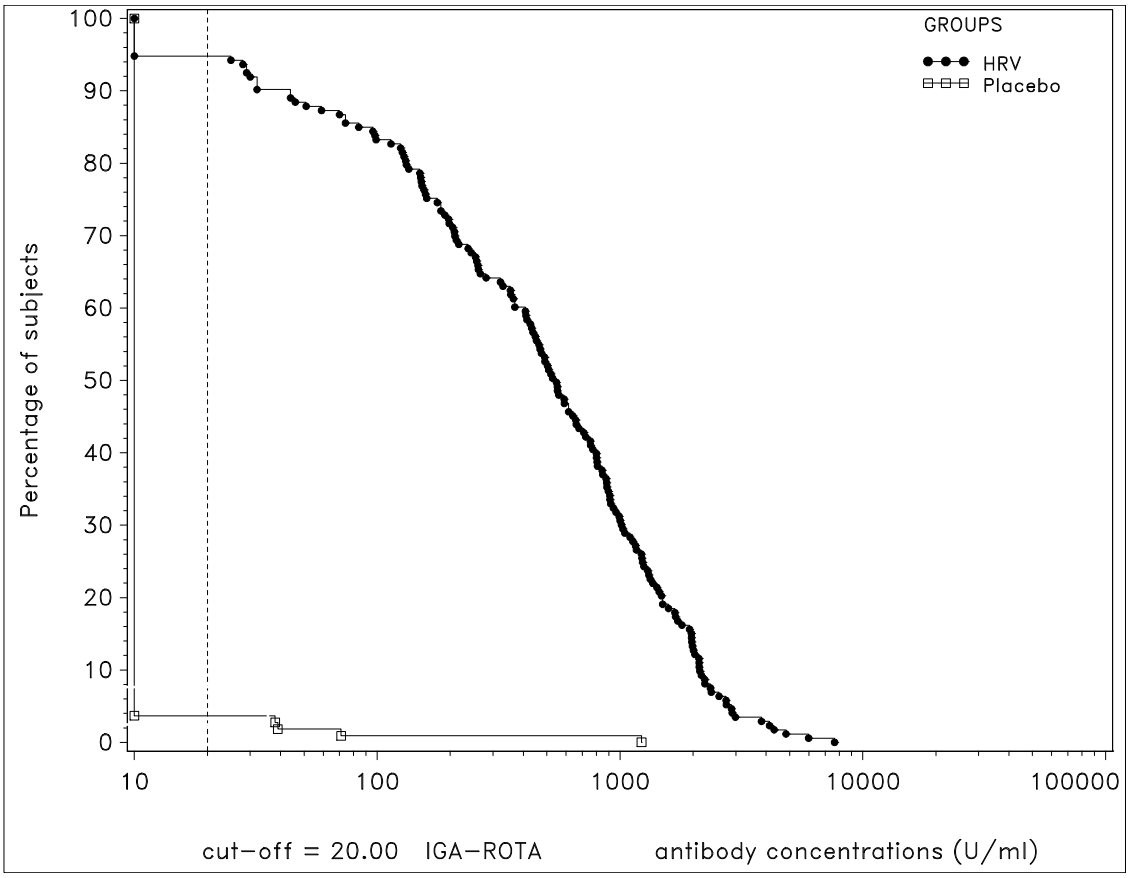
				GMC		
					95% CI	
Country	**Group**	**Timing**	**N**	**value**	**LL**	**UL**
(Each country)	**HRV**	**PII(M3-M4)**				
	Placebo	**PRE** **PII(M3-M4)**				
Pooled countries	**HRV**	**PII(M3-M4)**				
	Placebo	**PRE** **PII(M3-M4)**				

Notes:
N = number of subjects who are seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PRE = pre-vaccination
PII(M3-M4) = blood sample taken one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)

9.3.1.1.1. Reverse cumulative curves for anti- rotavirus IgA antibody concentrations

Distribution of antibody concentrations at the post-vaccination blood sampling at visit 3 will be presented graphically using reverse cumulative curves for each group (HRV and placebo) as in Table 55. These graphs will be presented for pooled countries on the ATP cohort for immunogenicity.

Table 55 Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at Visit 3 – Pooled countries - ATP cohort for immunogenicity



Source: Appendix Table III.A

9.3.1.2. Concomitant vaccination antibody concentration or titre

For the concomitant vaccination, the following tables will be generated separately for Czech Republic, Germany, Finland, France, Italy, and Spain:

Table 56 GMC and seropositivity/seroprotection rates for anti- (each vaccine antigen) antibody - Czech Republic (Germany; Finland; France; Italy; Spain) - ATP cohort for immunogenicity (Total vaccinated cohort for the reactogenicity and immunogenicity subset, if applicable)

				≥cut-off				GMT/GMC		
						95%CI			95%CI	
Country	Group	Timing	N	n	%	L.L.	U.L.	value	L.L.	U.L.
(Each country)	HRV									
	Placebo									

Notes:
N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI, L.L and U.L = lower and upper limits of the 95% CI
Anti-PRP: cut-off = 0.15µg/ml and 1 µg/ml (with 3 decimals for GMC)
Anti-D: cut-off = 0.1 IU/ml (with 3 decimals for GMC)
Anti-T: cut-off = 0.1 IU/ml (with 3 decimals for GMC)
Anti-PT, anti-FHA and anti-PRN: cut-off = 5 EL.U/ml (with 1 decimal for GMT)
Anti-HBs: cut-off = 10 mIU/ml (with 3 decimals for GMC)
Anti Polio type1, 2 and 3: cut-off = 8 (with 1 decimal for GMT)
Anti -4, Anti-6B, Anti-9V, anti-14, anti-18C, anti-19F, anti-23F Pneumoccocal antibody: cut-off =0.05µg/ml and 0.2 µg/ml (with 2 decimal for GMC)
Anti-PSC: cut-off = 0.3 µg/ml (with 2 decimals for GMC)
Anti- SBA-MenC: cut-off = 1:8 dilution (with 1 decimal for GMT)

The distribution of the concomitant antibody titers/concentration one month after dose 3 for Czech Republic, Germany, Finland, France, Italy, Spain and one month after dose 2 Finland, Italy, Spain will be displayed using reverse cumulative curves such as in Table 55.

9.3.2. Between group assessment

9.3.2.1. Anti-Rotavirus IgA

The asymptotic standardised 95% CI for the difference in the proportion of subjects who seroconverted after dose 2 between HRV and placebo groups will be computed for pooled countries on the ATP cohort for immunogenicity.

Table 57 Difference in percentage of subjects who seroconverted for anti-rotavirus IgA antibody after Dose 2 between HRV and placebo groups – pooled countries - ATP cohort for immunogenicity

						Difference in seroconversion rate			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
HRV			Placebo			HRV minus Placebo			

Notes:
N = number of subjects with available results

% = percentage of subjects who seroconverted one to two months after Dose 2 of HRV vaccine or placebo (Visit 3)
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

9.3.2.2. Concomitant vaccination

The asymptotic standardised 95% CI for the difference in seropositivity/seroprotection rate at one month after dose 2 of routine childhood vaccination will be computed for Finland, Spain and Italy, as in Table 58 for each concomitant vaccine administered, on the ATP cohort for immunogenicity.

The same table will be generated for the difference in seropositivity/seroprotection rate one month after dose 3 of routine childhood vaccination, for each country (for Czech Republic, France, Finland, Germany, Spain, Italy) and for each concomitant vaccine administered

Table 58 Difference in seropositivity/seroprotection rates one month after dose 2 (3) of routine childhood vaccination between placebo and HRV groups, for Anti- *(Each antigen)* - Czech Republic (Germany; Finland; France; Italy; Spain) - ATP cohort for immunogenicity

							Difference in seropositivity (seroprotection) rate			
							Anti- *(Each antigen) (cut-off: unit)*			
								Value	95% CI	
Country	Group	N	%	Group	N	%	Groups	%	LL	UL
(Each country)	Placebo			HRV			Placebo minus HRV			

Notes:
N = number of subjects with available results
% = percentage of subjects who are seropositive (seroprotected) one months after Dose 2 (3) of childhood routine vaccination
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

The 95% CI for the ratio of GMCs one month after dose 2 (Dose 3) of routine childhood vaccination between placebo and HRV groups will be computed (using a one-way ANOVA model on the logarithm10 transformation of the titers).

Table 59 Ratio of anti-(*each antigen*) antibody GMT/Cs, one month after the second (third dose) of routine childhood vaccination between placebo and HRV groups - Czech Republic (Germany; Finland; France; Italy; Spain) - ATP cohort for immunogenicity

							Ratio of GMT/Cs			
Country	Group	N	GMT/C	Group	N	GMT/C	Group ratio	Value	95 % CI L.L	U.L
(Each country)	Placebo			HRV			Placebo over HRV			

Notes: N = number of subjects with available results
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit

9.4. Efficacy analysis

Total vaccinated cohort:

- analysis from Dose 1 of HRV vaccine or placebo up to Visit 5 will be done on the Total vaccinated cohort. Analysis of the second and combined efficacy follow-up periods will not be performed.
- analysis from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 2 of HRV vaccine or placebo will be done on the Total vaccinated cohort.
- analysis from Dose 1 of HRV vaccine or placebo up to before Dose 2 of HRV vaccine or placebo will be done on the Total vaccinated cohort.

As an introduction to the efficacy analysis, the number of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 of HRV vaccine or placebo up to Visit 5 is presented in Table 60. This analysis will be performed for pooled countries on the Total vaccinated cohort (Dose 1 up to Visit 5).

Table 60 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 of HRV vaccine or placebo up to Visit 5 - Pooled countries - Total vaccinated cohort

Time point	Group	N	n	%	95%CI LL	UL
From Dose 1 up to Visit 3	(Each group)					
After Visit 3 to Visit 5	(Each group)					

Source: Appendix Table IIB, V.A and V.B
N = number of subjects included in each group
n/% = number/percentage of subjects with vaccine virus in at least one stool sample collected in case of GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit

Only RV GE episodes classified positive for RV caused by the circulating wild-type RV strains will be included in the below tables related to RV GE episodes.

A global overview of the number of GE episodes and RV GE episodes reported by the subjects during each efficacy follow-up period (first, second and combined efficacy periods) is provided for each group, for pooled countries on the ATP cohort for efficacy, as in Table 61. The same analysis will be provided for the Total vaccinated cohort (Dose 1 up to Visit 5, Dose 1 up to 14 days post Dose 2 and Dose 1 up to before Dose 2).

Table 61 Percentage of subjects who reported GE episodes and RV GE episodes during each efficacy follow-up period - Pooled countries - ATP cohort for efficacy (Total vaccinated cohort)

Event	Total number of episodes reported	HRV n %	Placebo n %
(each efficacy follow-up period)		**N =**	**N =**
GE	1 2 … Any		
RV GE	1 2 … Any		

Source: Appendix Table IIB, V.A and V.B
N = number of subjects included in each group, for the considered efficacy follow-up period
n/% = number/percentage of subjects reporting the specified total number of episode in the considered efficacy period
Any = number and percentage of subjects reporting at least one specified episode in the considered efficacy period

Table 62 presents the number of GE episodes with no stools collected or with no available stool results. This analysis will be provided for each group, for pooled countries and for each efficacy follow-up period (first, second and combined efficacy periods), on the ATP cohort for efficacy. The same analysis will be provided for the Total vaccinated cohort (Dose 1 up to Visit 5, Dose 1 up to 14 days post Dose 2 and Dose 1 up to before Dose 2).

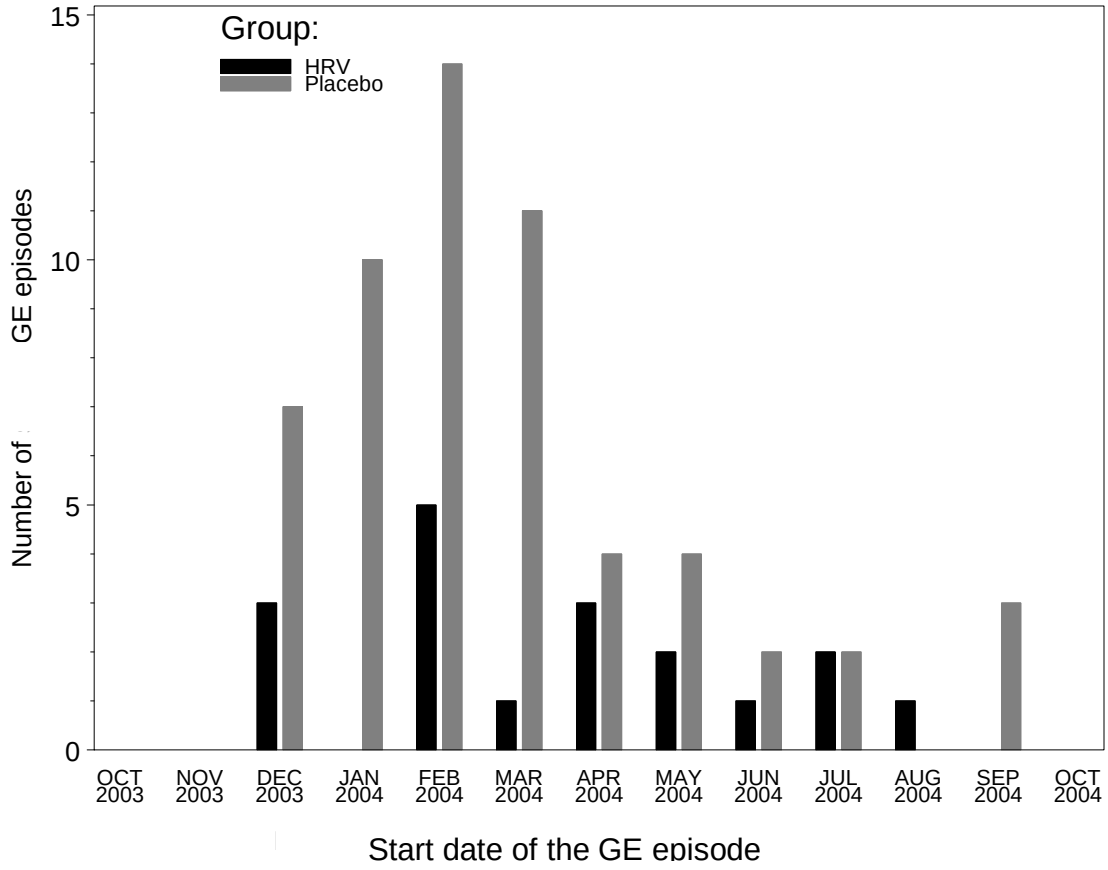
Table 62 Percentage of GE episodes with no available stool results during each efficacy follow-up period - Pooled countries - ATP cohort for efficacy (Total vaccinated cohort)

Category	HRV n	%	Placebo n	%	Total n	%
(each efficacy follow-up period)	**N'=**		**N'=**		**N'=**	
No stools collected **Stools collected but no results available** **No stool results available**						

Source: Appendix Table IIB, V.A and V.B
N'= number of GE episodes reported in the considered efficacy period
n/%= number/percentage of GE episodes reported in the considered efficacy period within the specified category

The seasonal distribution of GE episode and RV GE episode will be presented as in Table 63. This analysis will be performed per group, for each country and for pooled countries on the ATP cohort for efficacy (first and second efficacy period).

Table 63 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 5 (after Visit 5 up to Visit 7) - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - ATP cohort for efficacy



All GE episodes reported during the efficacy follow-up period are presented by severity using the 20-point Vesikari scale as in Table 64 and using the 24-point Clark scale as in Table 65. These analysis will be provided for each group, for pooled countries and for each efficacy follow-up period (first, second and combined efficacy periods) on the ATP cohort for efficacy. The same analysis will be provided for the Total vaccinated cohort (Dose 1 up to Visit 5, Dose 1 up to 14 days post Dose 2 and Dose 1 up to before Dose 2).

Table 64 Number of GE episodes and RV GE episodes reported during each efficacy follow-up period, by severity using the 20-point Vesikari scale – Pooled countries - ATP cohort for efficacy (Total vaccinated cohort)

Event	Severity using the 20-point Vesikari scale	HRV n %	Placebo n %
(each efficacy follow-up period)			
GE	Mild (1-6) Moderate (7-10) Severe (≥11) Any		
RV GE	Mild (1-6) Moderate (7-10) Severe (≥11) Any	-	

Source: Appendix Table IIB, V.A and V.B
n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported during the considered efficacy period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy period

Table 65 Number of GE episodes and RV GE episodes reported during each efficacy follow-up period, by severity using the 24-point Clark scale - ATP cohort for efficacy

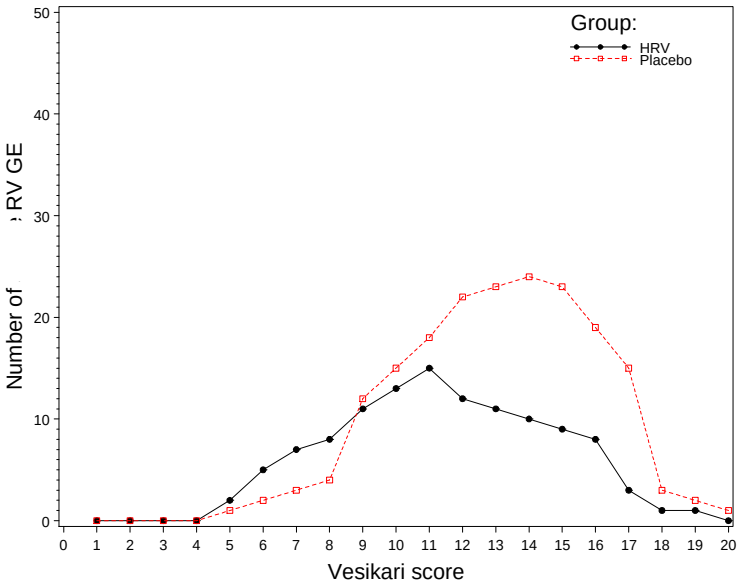
Event	Severity using the 24-point Clark scale	HRV n %	Placebo n %
(each efficacy follow-up period)			
GE	Mild (2-8) Moderate (9-16) Severe (≥17) Any		
RV GE	Mild (2-8) Moderate (9-16) Severe (≥17) Any		

Source: Appendix Table IIB, V.A and V.B
n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported during the considered efficacy period
Any = any specified symptom reported, regardless of Clark severity scale, in the considered efficacy period

A graph as in Table 66 will be drawn to show the number of subjects with RV GE according to severity using the 20-point Vesikari scale. A similar Graph will be drawn to show the number of subject with RV according to the 24-point Clark Scale.

These analysis will be provided for each group, for pooled countries on the ATP cohort for efficacy (first, second and combined efficacy periods). These analyses will also be provided for the Total vaccinated cohort (Dose 1 up to Visit 5).

Table 66 Distribution of Vesikari (Clark) score for RV GE episodes – Pooled countries – ATP cohort for efficacy (Total vaccinated cohort : Dose 1 up to Visit 5)



The percentage of subjects with RV GE episodes will be presented by G serotype and P genotype as in Table 67. This analysis will be provided for each group, for pooled countries and for each efficacy follow-up period (first, second and combined efficacy periods), on the ATP cohort for efficacy. The same analysis will be provided for the Total vaccinated cohort (Dose 1 up to Visit 5, Dose 1 up to 14 days post Dose 2 and Dose 1 up to before Dose 2).

Table 67 Percentage of subjects with RV GE episodes reported during each efficacy follow-up period, by G serotype and P genotype – Pooled countries - ATP cohort for efficacy (Total vaccinated cohort)

	HRV		Placebo	
Serotype	**n**	**%**	**n**	**%**
(each efficacy follow-up period)	**N=**		**N=**	
Any				
G1/P8 wild type				
….				

Source: Appendix Table IIB, V.A and V.B
N = number of subjects included in each group, for the considered efficacy period
n/% = number/percentage of subjects reporting at least once the specified serotype in the considered efficacy period
Any = number of subjects reporting at least one RV GE episode, whatever the serotype, in the considered efficacy period

The number of RV GE episodes will be presented by G serotype and P genotype as in Table 68. These analysis will be provided for each group, by country, for pooled countries and for each efficacy follow-up period (first, second and combined efficacy periods), on the ATP cohort for efficacy. The same analysis will be provided for the Total vaccinated cohort (Dose 1 up to Visit 5, Dose 1 up to 14 days post Dose 2 and Dose 1 up to before Dose 2).

Table 68 Number of RV GE episodes reported during each efficacy period, by G serotype and P genotype - Pooled countries (Czech Republic; Germany; Finland; France; Italy; Spain) - ATP cohort for efficacy (Total vaccinated cohort)

Serotype	**HRV**		**Placebo**	
	n	**%**	**n**	**%**
(each efficacy follow-up period)	**N'=**		**N'=**	
G1 wild type				
G2				
G4 and G9				
….				

Source: Appendix Table IIB, V.A and V.B
N'= number of RV GE episodes reported in the considered efficacy period
n/%= number/percentage of RV GE episodes reported in the considered efficacy period, by serotype

Table 69 presents a summary of characteristics for the RV GE episodes reported by main serotype (i.e. G1, non G1,…) and overall. The categories in Table 69 are defined according to the Vesikari scale. The same computation will also be generated on the basis of categories defined according to the Clark scale such as in Table 70.

These analysis will be provided for each group, for pooled countries for the ATP cohort for efficacy (first, second and combined efficacy periods). These analyses will also be provided for the Total vaccinated cohort (Dose 1 up to Visit 5). Similar table will also be generated for GE episodes.

Table 69 Characteristics (based on Vesikari scale) of RV GE episodes reported during each efficacy follow-up period, by main serotype and overall – Pooled countries - ATP cohort for efficacy (Total vaccinated cohort : Dose 1 up to Visit 5)

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Source: Appendix Table IIB, V.A and V.B

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

Table 70 Characteristics (based on Clark scale) of RV GE episodes reported during each efficacy follow-up period, by main serotype and overall - – Pooled countries - ATP cohort for efficacy (Total vaccinated cohort : Dose 1 up to Visit 5)

			(For each efficacy follow-up period and combined efficacy periods)			
			HRV		Placebo	
Serotype	Characteristics	Parameters or categories	Value or n	%	Value or n	%
		N'		-		-
(Main serotype and overall)	Clark severity score	Mean		-		-
		SD		-		-
		Median		-		-
		Minimum		-		-
		Maximum		-		-
	Duration of looser than normal stools (days)	0 day				
		1-4 days				
		5-7 days				
		> 7 days				
	Maximum number of than normal stools/day	0				
		2-4				
		5-7				
		> 7				
	Duration of vomiting (days)	0 - 1 day				
		2 day				
		3-5 days				
		> 5 days				
	Maximum number of episodes of vomiting/24day	0				
		1-3				
		4-6				
		> 6				
	Maximum fever reported /day (measured rectally)	< 38.0°C				
		38.0-38.2°C				
		38.3-38.7°C				
		≥ 38.8°C				
	Duration of fever (days)	0 day				
		1-2 day				
		3-4 days				

		≥ 5 days				
	Behavioral symptoms	**Behave as usual** **Irritable/ less playful** **Lethargic/listless** **Seizures**				
	Duration of behavioral symptoms	**0** **1-2** **3-4** **≥ 5**				

Source: Appendix Table IIB, V.A and V.B
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

Table 71 summarizes by group the follow-up in years during each efficacy period.

Follow-up is derived

- from 2 weeks after the second dose of HRV vaccine or placebo and the end of the first efficacy follow-up period or the last contact for the first efficacy follow-up period,
- from the end of the first efficacy follow-up period and the end of the second efficacy follow-up period or the last contact for the second efficacy follow-up period,
- from 2 weeks after the second dose of HRV vaccine or placebo and the end of the second efficacy follow-up period or the last contact for combined efficacy follow-up periods,

This table will also be generated for pooled countries, on the ATP cohort for efficacy and on the Total vaccinated cohort (Dose 1 up to Visit 5, Dose 1 up to 14 days post Dose 2 and Dose 1 up to before Dose 2).

Table 71 Duration (in years) of each efficacy follow-up period – Pooled countries - ATP cohort for efficacy (Total vaccinated cohort)

Duration (years) of follow-up period	**HRV**	**Placebo**
(each efficacy follow-up period)	**N=**	**N=**
Total **Mean** **Minimum** **Q1** **Median** **Q3** **Maximum**		

Source: Appendix I.C
N= Number of subjects included in each group in the considered efficacy period

Total= sum of follow-up period expressed in year for the considered efficacy period
Q1 = 25th percentile
Q3 = 75th percentile

The following Table will be generated for each country and for pooled countries, on the ATP cohort for efficacy:

Table 72 Number of subjects vaccinated before the RV season - Czech Republic (Germany; Finland; France; Italy; Spain; pooled countries) - ATP cohort for efficacy

		HRV		Placebo		Total	
COUNTRY	**Vaccinated before the RV season**	**n**	**%**	**n**	**%**	**n**	**%**
Czech Republic	Yes					146	49.0
	No					152	51.0
Finland	Yes					184	6.4
	No					2681	93.6
France	Yes					19	13.1
	No					126	86.9
Germany	Yes					28	9.9
	No					256	90.1
Italy	Yes					0	0.0
	No					25	100
Spain	Yes					0	0.0
	No					339	100
Overall total	Yes					377	9.5
	No					3579	90.5

Source: Appendix table I.C

Table 73 presents the efficacy of the HRV vaccine.

Table 73 Percentage of subjects reporting any RV GE and efficacy of the vaccine during each efficacy follow-up period - ATP cohort for efficacy

	n/N					Vaccine Efficacy		
				95%CI		95%CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
HRV								
Placebo								

Source: Appendix Table IIB, V.A and V.B
N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in the considered efficacy period
%= percentage of subjects reporting at least one RV GE episode in the considered efficacy period
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit

Table 73 will also be generated:

- for severe (score ≥ 11 using the 20-point Vesikari scale) RV GE,
- for any and severe RV GE by main serotype (i.e. G1, non-G1,..),
- for hospitalization due to RV GE
- for medical attention due to RV GE
- for any and severe RV GE from dose 1 up to Visit 5
- for any and severe RV GE by country,
- efficacy against severe RV GE using the Clark system (score ≥ 16 using the 24 - point Clark scale)
- for any and severe RV GE from dose 1 up to 2 weeks after dose 2
- for any and severe RV GE from dose 1 up to before dose 2
- for any GE
- for hospitalization against any GE
- for any and severe RV GE by feeding criteria (breast fed at one dose at least, breast fed at none of the doses)
- for any and severe RV GE by serological status for IgA antibody concentration at Visit 3

In addition, Tables 74 and 75 will also be generated for pooled countries on the ATP cohort for efficacy. The same tables will be generated using the Clark scale (≥17, ≥18, ≥19, ≥20, ≥21, ≥22, ≥23, ≥24)

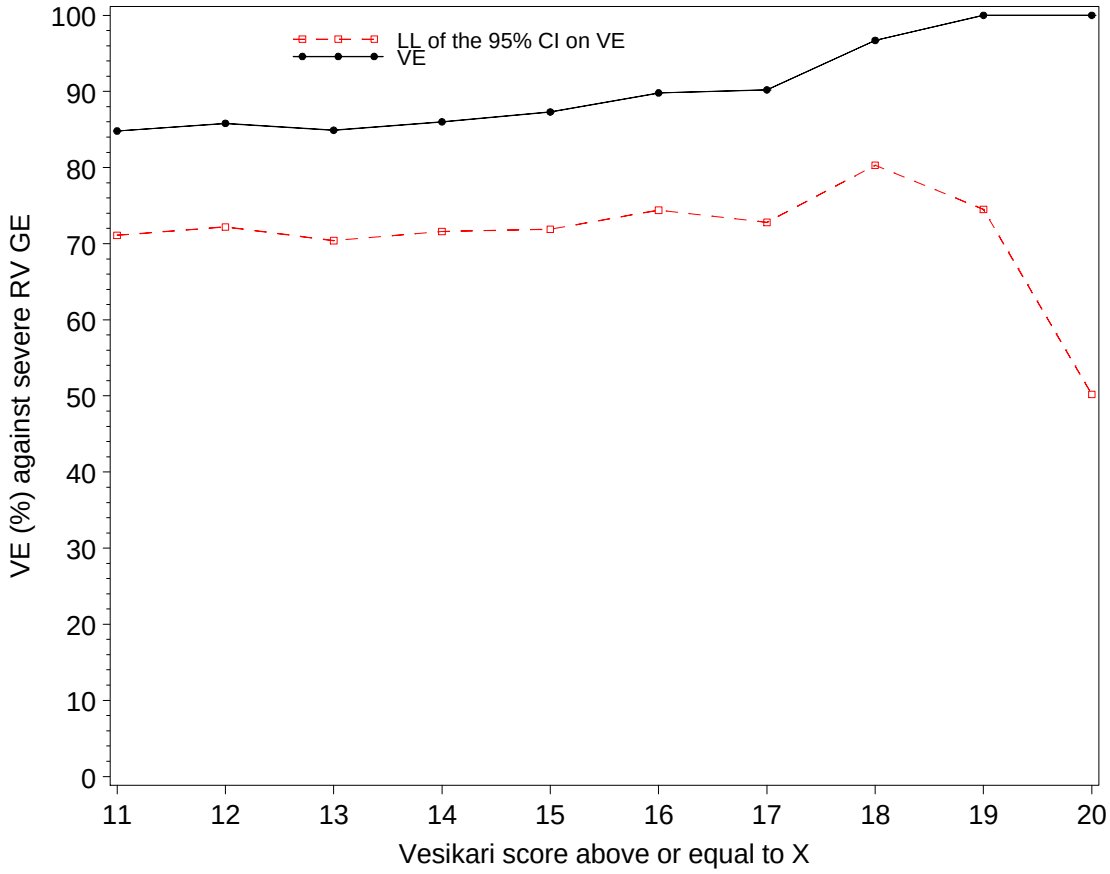
Table 74 Percentage of subjects reporting RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 – pooled countries - ATP efficacy cohort

Severity using Vesikari scale	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
≥11	HRV Placebo									
≥12	HRV Placebo									
≥13	HRV Placebo									
≥14	HRV Placebo									
≥15	HRV Placebo									
≥16	HRV Placebo									
≥17	HRV Placebo									
≥18	HRV Placebo									
≥19	HRV Placebo									
≥20	HRV									

	Placebo									

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode with a score ≥X on the Vesikari scale, in each group
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 75 Efficacy of the vaccine against RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 2 up to Visit 4 – pooled countries – ATP efficacy cohort



Moreover, the number of subjects reporting at least one RV GE episode during the efficacy follow-up periods (first efficacy, second efficacy and on combined efficacy follow-up) by serological status for IgA antibody concentration after Dose 2 will be computed and presented as in Table 76.

This table will also be generated for pooled countries on the ATP cohort for efficacy.

Table 76 Percentage of subjects in the HRV vaccine group reporting RV GE during the first efficacy follow-up period and on combined efficacy periods, by status of anti-rotavirus IgA antibody concentration at Visit 3 – Pooled countries - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 3	N	n	%	95%CI	
				LL	UL
(first efficacy follow-up period and combined efficacy follow-up period periods)					
Negative Positive Unknown					

Source: Appendix Table III.A, IIB, V.A and V.B
N = number of subjects included in the HRV vaccine group with the specified status for anti-rotavirus IgA antibody concentration at 1-2 months after Dose 2 (visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration 1-2 months after Dose 2 (visit 3) reporting at least one RV GE episode during the considered efficacy period
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit

Exploratory time-to-event analysis will be performed. Table 77 will be generated for the endpoints mentioned below; VE will be derived as 1- Cox hazard ratio (ATP cohort for efficacy):

- RV GE during the first efficacy follow-up period
- RV GE due to G1 serotype during the first efficacy follow-up period
- RV GE due to non-G1 serotypes during the first efficacy follow-up period

The time will be censored at the last contact in the first efficacy follow-up period.

Table 77 Efficacy of the vaccine against any RV GE during the first efficacy follow-up period, by Cox – pooled countries - ATP cohort for efficacy

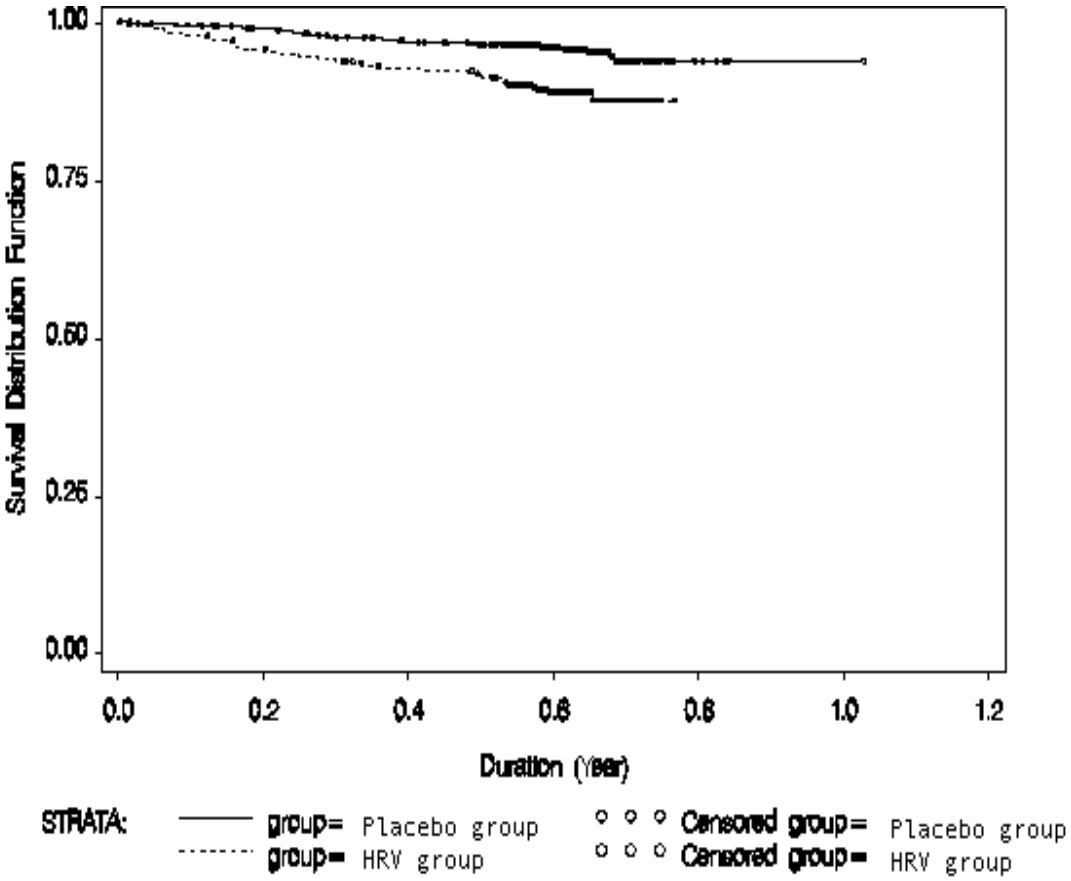
				n/T			Vaccine Efficacy		
			T		95%CI			95%CI	
Group	N	n	(year)	value	LL	UL	%	LL	UL
HRV **Placebo**									

Source: Appendix Table V.B and V.C
N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in the first efficacy period
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
n/T= person-year rate of RV GE in each group
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit

Kaplan Meier curves as shown below (ATP cohort for efficacy) will also be generated for the endpoint mentioned above.

Table 78 The Kaplan Meier curve for any RV GE / any RV GE due to G1 serotype / any RV GE due to non-G1 serotypes during the first efficacy follow-up period - ATP cohort for efficacy

(Y-axis can start at 0.50 if not readable):



10. ANNEX 2: ELIMINATION CODE CRITERION TO USE

Elimination from ATP cohorts for reactogenicity, immunogenicity and efficacy

1010 Subject or vaccine number not allocated
No subject allocated to the randomized number

1030 Study vaccine dose not administered AT ALL but subject number allocated

1040 Administration of intercurrent vaccine(s) forbidden in the protocol

1060 Randomization code broken

1070 Study vaccine dose not administered according to protocol :
- Replacement/ Wrong vaccine vial used NOT corresponding to the correct randomization group
- Subject number not in the randomization list and not requested by the sponsor (extra PID)

1500 Initially seropositive or initially unknown anti-rotavirus IgA antibody status on the day of Dose 1 of HRV vaccine or placebo

Elimination from ATP cohort for reactogenicity and from ATP cohort for immunogenicity

1035 Subjects for whom solicited symptoms were not to be collected and who were not planned to be bled for all blood sampling visits

Elimination from ATP cohort for immunogenicity

2010 Protocol violation linked to the inclusion/exclusion criteria including age and excluding codes mentioned below.

2040 Administration of any intercurrent medication forbidden by the protocol

2050 Underlying medical condition forbidden by the protocol

2060 Concomitant infection by rotavirus which may influence immune response (=rotavirus other than vaccine strain in GE stool samples collected up to Visit 3)

2070 Concomitant infection not related to the vaccine which may influence immune response

2080 Non compliance with vaccination schedules for HRV vaccine or placebo (dates of vaccination not corresponding to adapted protocol intervals or unknown vaccination dates)

2090 Non compliance with blood sampling schedules (dates of BS not corresponding to adapted protocol intervals or unknown BS dates)

2100 Serological results not available for the blood sample POST vaccination (including BS lost, Not Done, unable to test, absence of parallelism):

2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between eCRF and results, wrong labelling in BS)

Important remark: if code 2100 is attributed to a subject, codes 2080 and/or 2090 should not be assigned to the same subject

Elimination from ATP cohort for efficacy – firt, second and combined 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 other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response

Elimination from ATP cohort for efficacy – second period

4020	Subjects not entered into the surveillance period of the first efficacy follow-up period

11. ANNEX 3: STATISTICAL METHODS

11.1. Confidence interval for a proportion within a group

Let θ, the parameter used for indicating the proportion of subjects in a (infinite) target population developing a specified characteristic within a specified follow-up period after an assumed vaccination. Let N, the size of a randomly selected sample from this population. If n is the number of subjects presenting a given characteristic among these N subjects, the true percentage of subjects with the characteristic ('θ') can be estimated by (n/N)*100. Its exact (1-α)% confidence interval is obtained from:

$$\frac{1}{1+\frac{2*(N+1-n)}{2*n*finv(\alpha/2,2*n,\ 2*(N+1-n))}}$$ as the lower boundary

and

$$\frac{1}{1+\frac{2*(N-n)}{(2*n+2)*finv((1-(\alpha/2)),2*n+2,\ 2*(N-n))}}$$ as the upper boundary.

where finv(probability, degrees of freedom 1, degrees of freedom 2) returns the inverse of the F probability distribution and α is the type I error rate.

11.2. Confidence interval for a geometric mean within a group

Let m the parameter used for indicating the median of the titers obtained after an assumed vaccination in a (infinite) target population. Let N the size of a randomly selected sample from this population. If T_i is the antibody titer measured for a subject i (i=1,...., N), then, assuming a log normal distribution for T_i, the true median is derived from the geometric mean titer as

$$GMT = 10^{\left(\sum_{i=1}^{N}\log_{10}(T_i)\Big/N\right)}$$

and its (1-α)% confidence interval is obtained from

$$LL = 10^{(LL^*)} \text{ with } LL^* = GMT - tinv(1-(\alpha/2), N-1)*\left(SSD/(N*(N-1))\right)^{1/2}$$

$$UL = 10^{(UL^*)} \text{ with } UL^* = GMT + tinv(1-(\alpha/2), N-1)*\left(SSD/(N*(N-1))\right)^{1/2}$$

as lower limit and upper boundary, respectively

where tinv(p, N-1) returns the p^{th} percentile of the Student's t distribution with (N-1) degrees of freedom, α is the type I error rate and SSD is the sum of the squared deviations on the $\log_{10}$ transformed antibody titers.

11.3. Confidence interval for a vaccine efficacy

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{rn2}$$

where n1 = number of cases in the vaccine group
N1 = number of subjects in the vaccine group

n2 = number of cases in the placebo group

N2 = number of subjects in the placebo group

N1/N2 = r

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 binomial 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 (refer to Annex 3 – section 11.1).

12. REFERENCES

Clark HF, Borian EF, Bell LM. Protective Effect of WC3 Vaccine Against Rotavirus Diarrhea in Infants During a Predominantlys Serotype 1 Rotavirus Season. *J. of Infectious Diseases 1988, 158(3): 570-86*

Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical diarrhoeal episodes. *Scand J Infect Dis.* 1990;22:259-67.

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

GlaxoSmithKline Biologicals

Study title

A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

Annex 3: 109810 (Rota-036 EXT Y3) to Clinical Study Report 102247 (Rota) 036

(Development Phase IIIb)

Indication Studied: Immunisation according to 0, 1 or 2-month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks at the time of the first dose.

Study initiation date:	12 February 2007
Study completion date:	09 July 2007
Date of Annex Report 3:	06 August 2009
Scope of the report	This report presents the efficacy and safety analysis data during the study period for the long-term follow-up starting from the end of second efficacy follow up period till the end of third RV season in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

Sponsor Signatory: [redacted] MD, Ph.D.
Medical Director
GlaxoSmithKline Biologicals, Finland

This study was performed in compliance with Good Clinical Practice including the archiving of essential documents.

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SYNOPSIS

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

Title of the study: A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

Principal investigator:
This study was conducted by 9 investigators in Finland. Prof. [redacted] at the [redacted] Finland, was identified as the principal co-ordinating investigator for this study.

Study centres: This was a multi-centre study conducted at 17 centres in Finland.

Publication (reference): Not published as of 06 August 2009.

Study period:	**Clinical phase:** IIIb
Study initiation date: 12 February 2007 Study completion date: 09 July 2007	

Objectives:

Primary:

- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to any Rotavirus Gastroenteritis (RV GE) episodes caused by the circulating wild-type RV strains during the follow-up period.

Secondary efficacy objectives:

The objectives during the study period for the long-term follow-up were:

- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to severe RV GE caused by the circulating wild-type RV strains.
- To assess if the administration of GSK Biologicals' HRV vaccine could prevent any and severe RV GE caused by the wild-type RV strain of type G1.
- To assess if the administration of GSK Biologicals' HRV vaccine could prevent any and severe RV GE due to non-G1 types.
- To assess if the administration of GSK Biologicals' HRV vaccine could prevent severe GE.

Secondary safety objectives:

- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of serious adverse events (SAEs) during the follow-up period.
- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of Intususception (IS) during the period from end of the second follow-up period up to the start of the study (retrospective follow-up).

Study design: Open, placebo-controlled, multi-centre study with two parallel groups: HRV vaccine group and placebo group. The study assessed the long-term efficacy and safety follow-up during the study period from the end of second efficacy follow up period till the end of third RV season in subjects who participated in the primary study of Rota-036 (eTrack No. 102247) in Finland.

Number of subjects:	**Total**	**HRV group**	**Placebo group**
Enrolled and vaccinated in the primary study in Finland (Total vaccinated cohort)	2890	1918	972
Total cohort for long-term follow-up	1613	1082	531

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

Number of subjects:	**Total**	**HRV group**	**Placebo group**
According -To-Protocol (ATP) cohort for efficacy for the long-term follow-up	1590	1065	525

Diagnosis and criteria for inclusion: A healthy male or female subject who had completed the second year efficacy follow-up of the primary study in Finland and for whom written informed consent was obtained from parents or guardians prior to the study start.

Study vaccine, dose, mode of administration, lot no.: Refer to the primary study report of Rota-036 for information on study vaccine, dose, mode of administration and lot nos. of the vaccine administered during the primary vaccination study.

Reference vaccine /Comparator, dose and mode of administration, lot no.: Refer to the primary study report of Rota-036 for information on reference vaccine, dose, mode of administration and lot nos. of the placebo administered during the primary vaccination study.

Duration of the study: Duration of the study from the end of second efficacy follow up period till the end of third RV season was approximately 6 months for each subject.

Criteria for evaluation:

Efficacy:

A GE episode was defined as occurrence of diarrhoea with or without vomiting. A severe GE/ RV GE episode was defined as an episode of GE/RV GE scored ≥11 on the 20-point Vesikari scoring system [Ruuska, 1990]. Diarrhoea was defined as passage of three or more looser than normal stools (loose or watery stools) within a day. Stool samples were tested by Enzyme Linked Immunosorbent Assay (ELISA) for RV detection. All stool samples that were RV positive were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) to determine the type.

Primary efficacy endpoint:

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

Secondary efficacy endpoint:

- Occurrence of severe RV GE caused by the wild-type RV strains during the study period for the long-term follow-up
- Occurrence of any and severe RV GE caused by the wild-type RV strain of type G1.
- Occurrence of any and severe RV GE due to non-G1 types.
- Occurrence of severe GE.

Safety:

Recording of SAEs including IS and mortalities during the follow-up period.

Secondary safety endpoint:

- Occurrence of mortality and SAEs during the study period for the long-term follow-up.
- Occurrence of mortality and IS during the period from the end of the second follow-up period of the primary study up to the start of this follow-up study.

Statistical methods: Analyses were performed as per protocol and the study's Reporting and Analysis Plan (RAP).

Analysis of demography: The analysis of demography was performed on the ATP cohort for efficacy and the total cohort. The distribution of subjects enrolled among the study centres was tabulated as a whole and per group. The mean, range and standard deviation of age in months was calculated as a whole and per group. The racial and gender composition was also tabulated.

Analysis of efficacy: The primary analysis of efficacy was performed on the ATP cohort for efficacy. For each efficacy endpoint, the percentages of subjects reporting at least one episode were calculated between groups using two-sided Fisher's exact test (significance level of $\alpha = 0.05$). The vaccine efficacy (VE) rate for each efficacy endpoint was calculated with its 95% CI. Exploratory analysis on VE was also performed

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

against severe RV GE with score >16 on the Clark's scale, RV GE requiring medical attention and all cause GE.

Analysis of Safety: The analysis of safety was based on the Total cohort. Serious adverse events and mortalities reported during the follow-up period of the study were summarised by group. Information on retrospective deaths, IS and GE were also summarised by group.

Summary:

Demography:

In the ATP cohort for efficacy, the mean age at the end of this long term follow-up period was 31.2 months in the HRV vaccine group (range: 28-35 months) and 31.3 months in the placebo group (range: 28-36 months), respectively. Majority of the subjects were of White-Caucasian or of European heritage (99.6% in the HRV vaccine group and 100% in the placebo group). Females constituted 46.9% of the subjects in the HRV vaccine group and 50.3% of the subjects in the placebo group.

*Efficacy:*Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis).

Primary endpoint

During the long-term follow-up period:

- Four (0.4%) subjects in the HRV vaccine group and 3 (0.6%) subjects in the placebo group reported any RV GE during the long-term follow-up period (p-value 0.691). VE against any RV GE was 34.3% (95% CI: -348.7.6%; 88.9%).

Synopsis Table 1: Vaccine efficacy against any RV GE caused by the circulating wild type RV

			n/N			VE			
				95% CI			95% CI		
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	1065	4	0.4	0.1	1.0	34.3	-348.7	88.9	0.691
Placebo	525	3	0.6	0.1	1.7	-	-	-	-

N = number of subjects included in each group
n (%) = number (%) of subjects reporting at least one RV GE episode in the considered efficacy period
95% CI = 95% Confidence interval; L.L = Lower limit; U.L = upper limit
p value =Two-sided Fisher Exact test

Secondary Endpoints

During the long-term follow-up period:

- None of the subjects in the HRV vaccine group reported any RV GE, caused by G1 type when compared to 2 (0.4%) subjects reporting an RV GE episode in the placebo group (p-value 0.109). The VE against any RV GE caused by G1 type was 100.0% [95% CI: -162.5; 100.0%].
- Four (0.4%) subjects in the HRV vaccine group and 1 subject (0.2%) in the placebo group reported any RV GE episodes, caused by the non-G1 types (G2 and G9).
  - Three (0.3%) subjects in the HRV vaccine group and 1 subject (0.2%) in the placebo group reported any RV GE episodes caused by the G2 type.
  - One (0.1%) subject in the HRV vaccine group reported any RV GE episode caused by the G9 type. None of the subjects in the placebo group reported an RV GE caused by the G9 type (p-value 1.000).

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

Synopsis Table 2: Vaccine efficacy against any RV GE caused by the RV types

RV Type	Group	N	n	n/N			VE			p-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
G1 type	HRV	1065	0	0.0	0.0	0.3	100.0	-162.5	100.0	0.109
	Placebo	525	2	0.4	0.0	1.4	-	-	-	-
Non-G1 type	HRV	1065	4	0.4	0.1	1.0	-97.2	-9610.8	80.5	1.000
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
G2 type	HRV	1065	3	0.3	0.1	0.8	-47.9	-7663.7	88.1	1.000
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
G9 type	HRV	1065	1	0.1	0.0	0.5	.	-	98.7	1.000
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-

N = number of subjects included in each group
n (%) = number (%) of subjects reporting at least one RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

- One (0.1%) subject in the HRV vaccine group and one (0.2%) subject in the placebo group reported severe RV GE (p-value 0.551). VE against severe RV GE was 50.7% (95% CI: -3769.6%; 99.4%).

Synopsis table 3: Vaccine efficacy against severe RV GE

Group	N	n	n/N			VE			p-value
			%	LL	UL	%	LL	UL	
HRV	1065	1	0.1	0.0	0.5	50.7	-3769.6	99.4	0.551
Placebo	525	1	0.2	0.0	1.1	-	-	-	-

N = number of subjects included in each group
n (%) = number (%) of subjects reporting at least one severe RV GE episode in the considered efficacy period
% = percentage of subjects reporting at least one severe RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

- None of the subjects in the HRV vaccine group reported severe RV GE episodes caused by G1 type when compared to one (0.2%) subject reporting a severe RV GE episode in the placebo group (p-value 0.330). The VE against severe RV GE caused by G1 type was 100.0% [95% CI: -1822.5%; 100.0%].
- One (0.1%) subject in the HRV vaccine group reported severe RV GE caused by the non-G1 (G2) type. None of the subjects in the placebo group reported severe RV GE caused the non-G1 (G2) type (p-value 1.000).

Synopsis Table 4: Vaccine efficacy against severe RV GE caused by RV types

RV type	Group	N	n	n/N			VE			p-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
G1 type	HRV	1065	0	0.0	0.0	0.3	100.0	-1822.5	100.0	0.330
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
Non-G1 type	HRV	1065	1	0.1	0.0	0.5	-	.	98.7	1.000
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-

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

RV type	Group	N	n	n/N			VE			p-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
G2 type	HRV	1065	1	0.1	0.0	0.5	-	.	98.7	1.000
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
p value = Two-sided Fisher Exact test

Exploratory endpoints

During the long-term follow-up period:

- One (0.1%) subject in the HRV vaccine group and two (0.4%) subjects in the placebo group reported RV GE episodes that required medical attention (p-value 0.255). The VE against RV GE that required medical attention was 75.4% [95% CI: -373.5%; 99.6%].
- A total of 15 (1.4%) subjects in the HRV vaccine group and 6 (1.1%) subjects in the placebo group reported severe GE due to all cause (p-value 0.817).

Synopsis Table 5: Vaccine efficacy against all cause severe GE

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	1065	15	1.4	0.8	2.3	-23.2	-287.7	54.8	0.817
Placebo	525	6	1.1	0.4	2.5	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting severe GE episode
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

Safety Results: The analysis on safety was performed on the Total cohort.

End of the second efficacy (year 2) follow-up period of the primary study to the start of this long-term follow-up study at Year 3.

- The percentage of subjects reporting GE from the end of the second efficacy follow-up period till the end of third RV season tended to be lower in the HRV vaccine group when compared to the placebo group (9.5% in the HRV vaccine group and 11.7% in the placebo group).

Serious Adverse Events:

- No fatal events were reported from the end of the second efficacy (year 2) follow-up period of the primary study to the start of this long-term follow-up study at Year 3.
- No IS cases were reported from the end of the second efficacy follow-up period of the primary study up to the start of this long-term follow-up study.

Long-term follow-up period of this study

During the long-term follow-up period of this study:

- Gastroenteritis was reported by one subject in the HRV vaccine group and one subject in the placebo group.
- Pneumonia was reported by two subjects in the placebo group.
- None of the SAEs reported were considered by the investigator to be causally related to vaccination and all SAEs reported were resolved.

Conclusions:

- Due to the low number of RV GE cases reported in both HRV vaccine group and placebo group, the vaccine efficacy cannot be assessed from the results of this study.

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

- Among the circulating RV GE types:
  - A total of three (75%) subjects in the HRV vaccine group reported RV GE episodes caused by the G2 type. One (25%) subject in the HRV vaccine group reported an RV GE episode caused by the G9 type.
  - A total of two (66.7%) subjects in the placebo group reported RV GE episodes caused by the G1 type and one (33.7%) subject reported an RV GE episode caused by the G2 type.
- Among the SAEs reported during the long-term follow-up period, GE was reported by two subjects (one subject each in the HRV vaccine and placebo groups).
- None of the SAEs reported during the long-term follow-up period were considered by the investigator to be causally related to vaccination and all SAEs reported were resolved.
- No IS cases or fatal events were reported from the end of the second efficacy follow-up period up to the start of this long-term follow-up study.
- No clinical concerns can be raised based on the available safety data.

Reference: Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for severity of diarrheal episodes. *Scand J Infect Dis.* 1990; 22:259-67.

Date of Annex Report 3: 06 August 2009

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
GCP	Good Clinical Practice
GE	Gastroenteritis
GSK	GlaxoSmithKline
GSM	Global Study Manager
HRV	Human Rotavirus
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IRB	Institutional Review Board
IS	Intussusception
LL	Lower Limit
RAP	Reporting and Analysis Plan
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious adverse event

SAS	Statistical Analysis System
SD	Standard Deviation
SOP	Standard Operating Procedure
TC	Total cohort
UL	Upper limit
VE	Vaccine Efficacy

GLOSSARY OF TERMS

According-to-Protocol (ATP) cohort for efficacy:	The ATP cohort for efficacy included all subjects from the ATP efficacy cohort of the second year follow-up who had entered into the efficacy surveillance period of this long-term follow-up study.
Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE was therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Completed:	Subjects who completed the study visit.
Diarrhoea:	Passage of three or more looser than normal stools (loose or watery stools), within a day.
Diary card:	Cards given to the parents /guardians by the investigator to record the occurrence of GE episodes.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the analysis.
Gastroenteritis:	Diarrhoea with or without vomiting.
Independent Data Monitoring Committee (IDMC):	The IDMC was responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Rotavirus gastroenteritis for efficacy analysis:	An episode of GE occurring during the long-term follow-up period in which RV other than vaccine strain was identified in a stool sample collected not later than 7 days after the onset of GE symptoms.
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.

Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with a score of ≥11 on a 20-point scoring system (Vesikari scoring system).
Seropositive:	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.
Subject:	Term used throughout the report to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.
Total cohort:	The total cohort included all subjects who participated in this follow-up study with at least one vaccine administration documented in the primary study.
Total vaccinated cohort of the primary study:	The total vaccinated cohort included all subjects with at least one study vaccine administration documented in the primary study.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the Study Report (including the synopsis), the names of the vaccines and/or medications will be written without the subscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	generic description
Rotarix™	Human Rotavirus vaccine

1. ETHICS

1.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study protocol, the informed consent, and other information that required pre-approval were reviewed and approved by a national IEC.

1.2. Ethical conduct of the study

This study was conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including the Somerset West, 1996 version of the Declaration of Helsinki.

1.3. Subject information and consent

Written informed consent was obtained from each subject's parent /guardian prior to the performance of any study-specific procedures. Electronic Case report forms (eCRFs) were provided for each subject's data to be recorded.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

This study was conducted by 9 investigators in Finland. Prof. [redacted] at the [redacted] Finland, was identified as the principal co-ordinating investigator for this study.

GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium was the study sponsor and was responsible for administration of the study including clinical trial supply management.

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician monitored the safety aspects of the human rotavirus (HRV) vaccine clinical development. In this monitor capacity, the IDMC periodically reviewed safety data from this long-term follow-up study.

3. INTRODUCTION

Rotavirus (RV) infections are the leading cause of severe acute diarrhoea in young children worldwide. Each year an estimated 527,000 children aged <5 years die from rotavirus diarrhoea with >85% of these deaths occurring in low-income countries of Africa and Asia [CDC, 2008]. In the European Union, the annual burden of rotavirus disease in children younger than 5 years of age is estimated at more than 200 deaths, over 87,000 admissions and almost 700,000 outpatient visits [Vesikari, 2007].

In Finland, the burden of disease attributable to childhood rotavirus infection was assessed from data on hospital admissions for acute gastroenteritis and from reported virological diagnoses of rotavirus from 1985 to 1995. The mean number of hospitalisations (3584 annually in children less than 5 years of age) corresponded to approximately 5.6% of the birth cohort. RV was estimated to be responsible for 54% of cases; accordingly, 3% of all children in Finland are hospitalised due to rotavirus diarrhoea [Vesikari, 1999].

Prevention by vaccination is considered to be critical for effective control of RV infection and to control the global burden associated with RV Gastroenteritis (GE), GSK Biologicals has developed an oral, live, attenuated human rotavirus (HRV) vaccine for immunisation of infants as a two-dose series in the first year of life. The HRV vaccine was developed from the parent G1P[8] 89-12 vaccine strain with proven efficacy [Bernstein, 1998]. The HRV vaccine has been extensively studied in Phase I, Phase II and Phase III clinical studies, and is currently licensed in over 100 countries worldwide.

The Rota-036 study (eTrack No. 102247) was conducted in six European Union countries with 2890 subjects participating from Finland. A two year efficacy follow-up was carried out and it was seen that the HRV vaccine reduced the overall burden of GE in the first year of life. The overall reactogenicity profile of the HRV vaccine was also mild with no increase in any solicited symptoms including fever, diarrhoea and vomiting as compared with the placebo during eight days after each dose.

The current study was a follow-up study, designed in Finland to assess the long-term efficacy and safety of the subjects primed with GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine during the primary vaccination study of Rota-036. The study was initiated 6 months after the end of the second efficacy follow-up period of the primary study during the third year of age of the subjects.

3.1. Primary objectives

- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to any Rotavirus Gastroenteritis (RV GE) episodes caused by the circulating wild-type RV strains during the follow-up period.

Refer to Section 4.11.1 for the definition of the primary endpoint.

3.2. Secondary objectives

Secondary efficacy objectives:

The objectives during the study period for the long-term follow-up were:

- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to severe RV GE caused by the circulating wild-type RV strains.
- To assess if the administration of GSK Biologicals' HRV vaccine could prevent any and severe RV GE caused by the wild-type RV strain of type G1.

- To assess if the administration of GSK Biologicals' HRV vaccine could prevent any and severe RV GE due to non-G1 types.
- To assess if the administration of GSK Biologicals' HRV vaccine could prevent severe GE.

Secondary safety objectives:

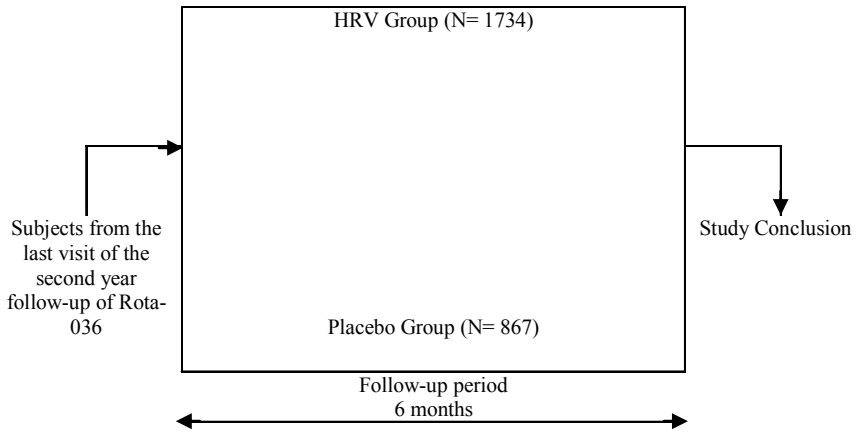
- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of serious adverse events (SAEs) during the follow-up period.
- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of Intusussception (IS) during the period from end of the second follow-up period up to the start of the study (retrospective follow-up).

Refer to Section 4.11.2 for definition of secondary endpoints.

4. INVESTIGATIONAL PLAN

4.1. Study design

4.1.1. Overall study design – Description



N = No. of subjects who were planned to be enrolled in the long-term follow-up

- Experimental design: Open, placebo-controlled long-term follow-up at approximately three years of age in subjects who participated in the primary study of Rota-036 (eTrack No. 102247) in Finland. For regulatory reasons, the primary study of Rota-036 was decoded. Hence, this long-term follow-up was an open study.
- Subjects who participated in the second year efficacy follow-up were followed up for efficacy and safety. A total of 2890 subjects from Finland participated in the primary study. Of these, 2601 subjects were expected to be enrolled in this long-term follow-up study from the two groups as follows:

– HRV vaccine group (N= 1734)

– placebo group (N= 867)

- Type of study: Efficacy and safety long-term follow-up study of Rota-036.
- Data collection: Remote Data Entry (RDE).
- All Adverse events (AE) leading to drop out were to be recorded.
- SAEs were to be actively collected by GSK during the long-term follow-up period.
- Any GE episode experienced by the subject during the study period of the long-term follow-up period was to be recorded.
- Any GE episode experienced by the subject during the end of the second follow-up period up to the start of the long-term follow-up for the third year (retrospective long-term follow-up) was to be reported by the subject's parent/ guardian.
- Any occurrence of mortality or IS during the end of the second follow-up period up to the start of the long-term follow-up for the third year (retrospective follow-up) was to be recorded.
- Duration of the study: All subjects were followed for a period of six months.

4.2. Study procedures

4.2.1. Outline of study procedures

Table 1 presents the outline of study procedures.

Table 1 List of study procedures

	Timing: Beginning of January 2007 up to the end of June 2007
Informed consent	●
Check of inclusion criteria at long-term follow-up time point	●
Check of elimination criteria	●
Medical history	●
Reporting of all GE since the last visit in the 2nd yr follow-up	●
Retrospective collection of cases of IS and mortality since the last visit in the 2nd yr follow-up	●
Collection of stool samples if the child developed GE	●
Reporting of all GE during the follow-up period	●
Reporting of SAEs during the follow-up period	●
Reporting of mortality during the follow-up	●
Reporting of AEs leading to subject withdrawal and drop out	●
Telephone contact or SMS	●
Return of GE diary cards	●
Diary card transcription by investigator	●
Study Conclusion	●

● is used to indicate a study procedure which required documentation in the eCRF.

It was the investigator's responsibility to ensure that the interval between the previous follow-up (at year two) and the current long-term follow-up visit was followed as closely as possible.

4.2.2. Intervals between study visits

Not applicable.

4.3. Selection of study population

At the time of initiation of the study, the investigator was to contact all subjects who completed the second year efficacy follow-up of the primary vaccination study (eTrack No.102247) from the centres in Finland. If at the time of initiation of the long-term study, any parent/guardian of the subject declined participation, refusal was documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information was entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.

A total of 2601 subjects were expected to participate in this study.

4.3.1. Inclusion criteria

All subjects were to satisfy the following criteria at study entry:

- A male or female who had completed the second year efficacy follow-up of the primary vaccination study (Rota-036, eTrack No.102247) in Finland.
- Written informed consent obtained from the parent or guardian of the subject.

4.3.2. Exclusion criteria

Not applicable. This study was a long-term efficacy and safety follow-up of all subjects who had completed the second year efficacy follow-up period and received the HRV vaccine or the placebo dose in the primary vaccination study of Rota-036 in Finland.

4.3.3. Elimination criteria

The following criteria were checked during the study and if any became applicable during the study, it did not require withdrawal of the subject from the study but it determined a subject's evaluability in the according-to-protocol (ATP) analysis.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the long-term follow-up.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the long-term follow-up. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)

- Administration of immunoglobulins and/or any blood products during the long-term follow-up period.

4.3.4. Contraindications to subsequent doses of vaccine

Not applicable for this long-term follow-up study. Refer to the primary study report for contraindications to subsequent doses of the vaccine administered.

4.3.5. Subject completion and withdrawal from study

4.3.5.1. Subject completion

A subject, whose parent/guardian was available for the concluding contact foreseen in the protocol, was considered to have completed the study.

4.3.5.2. Subject withdrawal from the study

A withdrawal from the study was defined as any subject who did not come back for the concluding visit foreseen in the protocol. The investigators attempted to contact these subjects who did not return for the scheduled visit or follow-up. Information gathered was specified in the Study Conclusion section of the electronic case report form. The following possible reasons were responsible for withdrawal of the subject from the study:

- SAE
- Non-serious adverse event
- Protocol violation
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Other (was to be specified).

4.3.5.3. Subject withdrawal from administration of the investigational product

Not applicable. Refer to the primary study report for the subject withdrawal due to administration of the investigational product.

4.4. Composition and administration of vaccines

4.4.1. Description of vaccines

Refer to the primary study report for the description of the vaccines (HRV vaccine and placebo) administered to the subjects.

4.4.2. Dosage and administration

Refer to the primary study report for the dosage and administration of study vaccines administered to the subjects included in the primary vaccination study.

4.4.3. Treatment allocation and randomisation

Not applicable for the long-term follow-up period presented in this report. Refer to the primary study report for details on treatment allocation and randomisation.

4.4.4. Blinding

This study was a long-term follow-up study of the Rota-036 study. Subjects who were part of the primary study in Finland were recruited for this study. The study was conducted in an open manner since the primary study was unblinded at the study end as per regulatory requirements.

4.5. Prior and concomitant medication /vaccinations

Not applicable for this long-term follow-up study. Refer to the primary study report for details of the prior and concomitant medications received by the subjects during the first two years of life.

4.6. Laboratory assays and time points

Not applicable for this efficacy and safety long-term follow-up study.

4.7. Assessment of immunogenicity variables

Not applicable since this study was designed to assess the long-term efficacy and safety of the HRV vaccine.

4.8. Assessment of efficacy variables

Follow-up of GE cases

GE was defined as diarrhoea with or without vomiting.

A retrospective long-term follow-up for the occurrence of GE episodes was conducted where the parents/guardians were asked to report any GE episode that occurred between the end of the second year efficacy follow-up up to the start of this long-term follow-up at year 3.

Active follow-up for occurrence of GE episodes was conducted during the follow-up period. Each subject's parent/guardian was contacted once every two weeks to check on the occurrence of any GE. This contact was made by telephone or short message service (SMS) using cellular phone. In case of unavailability of the subject’s parent/guardian at

the time of contact, at least one more attempt was to be made before the next planned contact.

Data collection for GE cases

The parents/ guardians were provided with diary cards to record any GE episode. For each suspected GE episode occurring during the study period, the GE diary card was to be completed by the parents/ guardians daily until the end of the GE symptoms.

The following information was recorded on the GE diary card daily during each suspected GE episode:

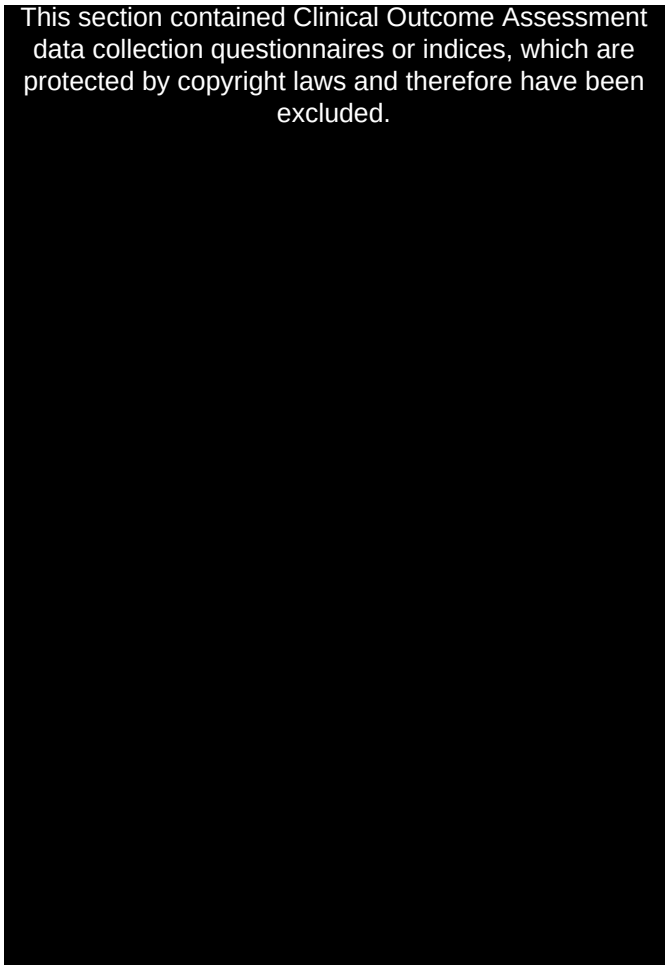
- Axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject.
- Rehydration or other medication given to the subjects during the GE episode.
- Medical attention sought for each GE episode (medical provider contact, advice, visit; emergency room contact or visit or hospitalisation)
- Behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or any seizure) and their duration.

The completed diary cards were collected by the study personnel. The investigator verified the returned completed GE diary card and transcribed the information into the appropriate sections of the eCRF, in English.

Vesikari scale for assessment of intensity of GE episodes

The information from the GE diary card was used to assess the intensity of the GE episodes using the 20-point Vesikari scale [Ruuska, 1990]. Based on the information in the GE diary card, points were assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalisation (hospitalised subjects were considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 2.

Table 2 The 20 - point scoring system to determine the intensity of GE episodes reported during the study



* The highest temperature recorded during the episode was to be scored.

For each episode of GE, a global score (sum of individual points) was calculated. The severity using the 20-points Vesikari scale was defined as below:

- A score < 7 was prospectively defined as mild,
- A score between 7 and 10 was prospectively defined as moderate,
- A score ≥11 was prospectively defined as severe.

Clark scale for assessment of intensity of GE episodes (exploratory evaluation)

The information from the GE diary card was also used to assess the intensity of the GE episodes using the 24-point Clark scoring system for an exploratory evaluation. In this scale, points were assigned at GSK Biologicals according to duration and intensity of diarrhoea, vomiting and fever, as well as on the intensity and duration of behavioral symptoms as shown in Table 3.

Table 3 The 24-point Clark scoring system to assess intensity of GE episodes

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode was scored.
§ Missing confirmed corresponded to the situation where the route for temperature was omitted in the eCRF and had not been recovered while addressing queries to the investigator

For each episode of GE, a global score (sum of individual points) was calculated. The severity using the 24-points Clark scale was defined as below:

- A global score < 9 was prospectively defined as mild,
- A global score between 9 and 16 was prospectively defined as moderate,
- A global score > 16 was prospectively defined as severe.

Medically attended visits

For each GE episode that the subject experienced, the subject's parents/guardians were asked if they received medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information was recorded in the eCRF.

Collection of stool samples during GE

For each GE episode occurring during the study period, a stool sample was to be obtained from the subject. The stool sample was to be collected as soon as possible after symptoms began but not later than 7 days after the onset of GE symptoms. A stool sample was to be collected for each separate diarrhoea episode. Two occurrences of diarrhoea were to be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. A second stool sample was to be collected if the first sample is insufficient (based on the discretion of the parent/ guardian).

The stool samples were to be stored in a home freezer until they were transferred rapidly to the investigator's laboratory. The stool samples were stored frozen at approximately –20°C or colder until shipped to [redacted] laboratory.

GE stool analysis

Stool samples collected during GE episodes were processed at the study site and transported to the [redacted] laboratory where further analysis was carried out for HRV detection using Dako IDEIA Enzyme Immuno Assay (EIA) Test.

If a stool sample tested positive for RV, the sample was to be tested by Polymerase Chain Reaction (PCR) in the [redacted] laboratory to determine the type. No additional testing was to be performed by the investigator without prior approval from GSK Biologicals'.

4.9. Assessment of safety variables

4.9.1. Adverse events

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.

An AE was any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Investigators followed-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event had resolved, subsided, stabilized, disappeared, the event was otherwise explained, or the subject was lost to follow-up;

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, ultrasound etc.) that were judged by the investigator to be clinically significant were recorded as AEs or SAEs if they met the definition of an AE, as defined in Section 4.9.1 or SAE, as defined in Section 4.9.2. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were reported as AEs or SAEs. The investigator exercised his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant. Clinically significant laboratory abnormalities were to be followed up until they had returned to normal, or a satisfactory explanation had been provided.

Assesment of AEs during the follow-up period

When an AE leading to subject withdrawal or dropout occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. All AEs leading to subject withdrawal were to be recorded on the Adverse Event form in the subject eCRF, irrespective of intensity or whether or not they were considered vaccination-related.

Any occurrence of mortality or IS during the end of the second follow-up period up to the start of the long-term follow-up for the third year (retrospective long-term follow-up) was to be recorded.

SAEs were actively collected by GSK during the long-term follow-up period.

A post-study AE/ SAE was defined as any event that occurred outside of the AE/ SAE detection period defined above. Investigators were not obligated to actively seek AEs or SAEs in former study participants.

Intensity of the AEs leading to subject withdrawal or drop out and SAEs

Based on their clinical judgement, the investigators assessed intensity of the reported AEs leading to drop out and SAEs, as follows:

1 (mild)	=	An AE/ SAE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE/ SAE which was sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE/ SAE which prevented normal, everyday activities. (In a young child, such an AE/ SAE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice).

Relationship between vaccination and AEs leading to drop out and SAEs

The investigators assessed the relationship between investigational product administered in the primary study and the occurrence of each event using their clinical judgement.

Causality of all AEs was assessed by the investigator using the following question: Was there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	The AE was not causally related to administration of the study vaccine(s). There were other, more likely causes and administration of the study vaccine(s) was not suspected to have contributed to the AE.
YES	:	There was a reasonable possibility that the vaccine(s) contributed to the AE.

GSK Biologicals' could request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE leading to drop-out or SAE. The investigator was obliged to assist.

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined "serious" (see Section 4.9.2 for definition of 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (was to be specified).
- Death

Outcome of AE/SAE

Outcome of any non-serious AE leading to subject withdrawal or any SAE reported during the entire study was assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving

- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

4.9.2. Serious adverse events

A SAE was any untoward medical occurrence that

- resulted in death,
- was life-threatening,
- required hospitalisation or prolongation of existing hospitalisation,
- resulted in disability/incapacity,
- was a congenital anomaly/birth defect in the offspring of a study subject,
- medical or scientific judgement was exercised in deciding whether reporting was appropriate in other situations, such as important medical events i.e. IS that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

The investigator inquired about the occurrence of SAEs at each contact during the study. SAEs were to be reported promptly to GSK once the investigator determined that the event met the protocol definition of an SAE. When a SAE occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.

The investigator then recorded all relevant information regarding the SAE on the SAE Report Form. The investigator or designate faxed the SAE reports to GSK Biologicals' Study Contact for reporting SAEs within 24 hours of his/her becoming aware of these events. In rare circumstances and in the absence of facsimile equipment, notification by telephone was acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone did not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours. Additional or follow-up information relating to the initial SAE report was also to be reported to the GSK Biologicals' Study Contact for reporting SAEs within 24 hours of receipt of such information. The investigator provided an assessment of causality at the time of the initial report. In the event of a death determined by the investigator to be related to vaccination, sending of the fax was to be accompanied by telephone call to the Study Contact for reporting SAEs. The standard Verbal Autopsy Questionnaire was to 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 was performed or not. The Standard Verbal Autopsy Questionnaire did not replace the written autopsy report.

Investigator safety reports were prepared for each SAE according to the current GSK policy and were forwarded to investigators as necessary. An investigator safety report was prepared for a SAE(s) that was both attributable to investigational product and unexpected. The purpose of the report was to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

If an investigator learnt of any SAE, including a death, at any time after a subject had been discharged from the study, and he/she considered the event reasonably related to the investigational product, the investigator was to promptly notify the Study Contact for reporting SAEs.

Assessment of SAEs leading to subject withdrawal or dropout

After the initial SAE report, the investigator was required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

New or updated information was recorded on the originally completed SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form was resent to GSK Biologicals within 24 hours of receipt of the follow-up information.

All SAEs documented at a previous contact and designated as not recovered/ not resolved or recovering/ resolving were to be reviewed at the end of the follow-up period.

4.9.2.1. Intussusception

Any occurrence of IS (symptoms of which include severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41 °C) during the end of the second follow-up period up to the start of the long-term follow-up for the third year was to be recorded retrospectively.

4.10. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, electronic case report form and safety reporting were reviewed with the investigators and their personnel responsible for the conduct of the study by the Company representative(s) prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy were 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 GlaxoSmithKline Biologicals Standard Operating Procedures (SOPs).

A Contract Research Organisation [Smerud Medical Research Finland] was employed to perform monitoring activities according to an agreed contract. The CRO responsibilities were conducted according to the SOPs agreed between GSK and the CRO.

Independent Audit statement:

No study specific audits were performed for this study.

4.11. Statistical methods

All analyses were performed as specified in the protocol and in the study reporting and analysis plan (RAP).

The analyses were performed using Statistical Analysis System (SAS) 9.1 and StatXact-Procs 7.0.

4.11.1. Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

4.11.2. Secondary endpoints

Efficacy endpoints

The endpoints during the study period for the long-term follow-up were as follows:

- Occurrence of severe RV GE caused by the wild-type RV strains during the study period for the long-term follow-up
- Occurrence of any and severe RV GE caused by the wild-type RV strain of type G1.
- Occurrence of any and severe RV GE due to non-G1 types.
- Occurrence of severe GE.

Safety endpoints

- Occurrence of mortality and SAEs during the study period for the long-term follow-up.
- Occurrence of mortality and IS during the period from the end of the second follow-up period of the primary study up to the start of this long-term follow-up study.

4.11.3. Determination of sample size

The primary objective of the study was to assess if two doses of GSK Biologicals' HRV vaccine could prevent any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

Subjects from Finland who completed the second year efficacy follow-up of the primary study were followed up for this study. A total of 2890 subjects from Finland participated in the primary study [Rota-036 (eTrack No. 102247)]. Assuming that up to 10% of the subjects might not have been willing to participate in this study; 2601 subjects were expected to be enrolled in this long-term follow-up study. Allowing for up to 10% of subjects who might not have been evaluable for analyses of the primary objective, 2340 subjects (1560 in HRV and 780 in placebo groups, respectively) were expected to be evaluable for the analysis of the primary objective.

Considering a 2:1 randomisation ratio and various incidence rates, Table 4 provides the power that the 95% CI for vaccine efficacy is above given limits.

Therefore, if the vaccine efficacy was truly 70% and if the incidence rate was 3.5%, the study would have had at least 80% power to observe that the lower limit of the 95% CI for the vaccine efficacy that was above 20%.

Table 4 presents the power to observe a 95% CI above various cut-offs according to various incidence rates and a true vaccine efficacy of 70% (power obtained from simulations using 1560 evaluable subjects in the HRV vaccine group and 780 evaluable subjects in the placebo group).

Table 4 Power to observe a 95% CI above various cut-offs according to various incidence rates and a true vaccine efficacy of 70% (power obtained from simulations using 1560 evaluable subjects in the HRV vaccine group and 780 evaluable subjects in the placebo group)

Incidence rate in the placebo group	True vaccine efficacy	Cut-off for the lower limit of the 95% CI on vaccine efficacy			
		0%	10%	20%	30%
Any Gastroenteritis					
3.5%	70%	95%	92%	86%	75%
1%	70%	45%	34%	30%	21%

4.11.4. Study cohorts /data sets analysed

Total cohort

The total cohort included all subjects who participated in this long-term follow-up study with at least one vaccine administration documented in the primary study:

ATP cohort for the analysis of efficacy

The ATP cohort for efficacy included all subjects from the ATP efficacy cohort of the second year follow-up who had entered into the efficacy surveillance period of this long-term follow-up study.

4.11.5. Derived and transformed data

Efficacy

An episode of GE was classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain was identified in a stool sample collected during the episode. A GE episode without a stool sample/result available was not considered in the analysis as an RV GE episode.

4.11.6. Analysis of demographics

The distribution of subjects enrolled among the study centres was tabulated as a whole and per group. The mean, range and standard deviation of age in months was calculated as a whole and per group. The racial and gender composition was also tabulated.

4.11.7. Analysis of efficacy

The primary analysis of efficacy was performed on the ATP cohort for efficacy.

Vaccine efficacy was calculated, with their 95% CI against:

- Any and severe RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.
- Any and severe RV GE due to G1 type caused by the circulating wild-type RV strains during the study period for the long-term follow-up.
- Any and severe RV GE due to non-G1 types during the study period for the long-term follow-up.
- Severe GE during the study period for the long-term follow-up.

The VE was defined as the percent reduction in the frequency of the relevant endpoint in vaccinated subjects compared to those subjects who received placebo. This was calculated as follows:

VE = (1- RR)*100 = (1 - (ARV/ARU))*100

Where:

Attack Rate in Unvaccinated Group (ARU) = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one severe RV GE episode / total number of subjects in the placebo group.

Attack Rate in Vaccinated Group (ARV) = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one severe RV GE episode / total number of subjects in the HRV vaccine group.

RR = relative risk = ARV/ARU.

The 95% CIs for VE were derived using a conditional to cases approach.

Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to calculate the percentages between HRV and Placebo groups.

4.11.8. Analysis of safety

The analysis of safety was based on the Total cohort.

Serious adverse events and mortalities reported during the long-term follow-up period of the study were summarised by group. Information on retrospective deaths, IS and GE were also summarised by group.

4.11.9. Interim analysis

Refer to the primary study report of Rota-036 for information on interim analyses performed until the end of the primary study. No interim analysis was planned for this long-term follow-up study.

4.12. Changes in the conduct of the study or planned analyses

4.12.1. Protocol amendments

No amendments were made to the study protocol.

4.12.2. Other changes

Analyses were performed as planned in the protocol and the study reporting and analysis plan (RAP) except the p-value for comparing groups with respect to efficacy was based on Fisher exact test instead of the two-sided asymptotic score test.

5. STUDY POPULATION RESULTS

5.1. Study dates

The first subject was enrolled in the study on 12 February 2007 and the last study visit was on 09 July 2007.

5.2. Subject eligibility and attrition from the study

5.2.1. Number of subjects

A total of 2,890 subjects from Finland were vaccinated in the primary study and received at least one dose of the HRV vaccine or placebo. Of these a total of 1,613 subjects in Finland (1082 subjects in the HRV vaccine group and 531 subjects in the placebo group) were included in this long-term follow-up study.

Supplement 1 presents the number of subjects enrolled at each centre.

5.2.2. Study completion and withdrawal from study

Table 5 presents the number of subjects enrolled, completed and withdrawn from the study with reasons for withdrawal for the total cohort.

Of the 1613 subjects enrolled in this long-term follow-up study, a total of 1592 subjects (1070 subjects in the HRV vaccine group and 522 subjects in the placebo group) completed the study.

A total of 21 subjects were study withdrawals. The reasons for withdrawal were as follows:

- One subject in the placebo group was withdrawn from the study due to a consent withdrawal by the parents. The withdrawal was not due to an AE.
- A total of 20 subjects (12 subjects in the HRV vaccine group and 8 subjects in the placebo group) were lost to follow-up. Subjects had completed the vaccination course in the primary study.

Table 5 Number of subjects enrolled, completed and withdrawn with reason for withdrawal (Total cohort)

	HRV	Placebo	Total
Number of subjects enrolled in this follow-up study	1082	531	1613
Number of subjects who completed the follow-up study	1070	522	1592
Number of subjects withdrawn	12	9	21
Reasons for withdrawal :			
Serious Adverse Event	0	0	0
Non-serious adverse event	0	0	0
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	0	1	1
Migrated/moved from study area	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	12	8	20

Enrolled = number of subjects who were enrolled in the follow-up study
Completed = number of subjects who completed follow-up study
Withdrawn = number of subjects who did not come for the follow-up study

5.2.3. Protocol deviations

Table 6 presents the number of subjects enrolled in the study as well as the number excluded from the ATP cohort for efficacy with reasons for exclusion.

Subjects could be attributed more than one elimination code; in the text, subjects are listed on the basis of the lowest elimination code.

Total cohort

Of the 2890 subjects enrolled and vaccinated in the primary study a total of 1613 subjects (1082 subjects in the HRV vaccine group and 531 subjects in the placebo group) were included in the Total cohort for this long-term follow-up study.

ATP cohort for efficacy

Of the 2890 subjects included in the Total vaccinated cohort (TVC) of the primary study, 1300 subjects were eliminated from the ATP cohort for efficacy in this long-term follow-up study, due to the following reasons:

- A total of 18 subjects (13 subjects in the HRV vaccine group and 5 subjects in the placebo group) were eliminated with code 1040 for having received a vaccine forbidden in the protocol.
- A total of 4 subjects (2 subjects in the HRV vaccine group and 2 subjects in the placebo group) were eliminated with the code 1070 in the primary study since for these subjects the study vaccine dose was not administered as defined in the protocol.
- Two subjects in the placebo group were eliminated with the code 1500 in the primary study because these subjects were initially seropositive for anti-rotavirus IgA antibodies and due to unknown status for anti- rotavirus IgA antibodies on the day of Dose 1 of the HRV vaccine or placebo.
- A total of 25 subjects (18 subjects in the HRV vaccine group and 7 subjects in the placebo group) were eliminated with the code 3010 in the primary study since they did not receive the full vaccination course (i.e. one of the 2 doses of HRV vaccine or placebo was not administered for these subjects).
- Three subjects (1 subject in the HRV vaccine group and 2 subjects in the placebo group) were eliminated with the code 3030 in the primary study since the GE stool samples of these three subjects collected from Dose 1 up to 2 weeks after Dose 2 were positive for RV other than the vaccine strain.
- A total of 14 subjects (9 subjects in the HRV vaccine group and 5 subjects in the placebo group) were eliminated with the code 4020 from the second efficacy follow-up period in the primary study because these subjects did not enter the surveillance period of the second efficacy follow-up.
- A total of 1234 subjects (810 subjects in the HRV vaccine group and 424 subjects in the placebo group) were eliminated with the code 5020 since these subjects did not enter the surveillance period of this long-term follow-up study.

Thus, the ATP cohort for efficacy for this long-term follow-up included 1590 subjects (1065 subjects in the HRV vaccine group and 525 subjects in the placebo group).

Table 6 Number of subjects enrolled into the study as well as the number excluded from ATP cohort for efficacy with reasons for exclusion in the follow-up period

	Total			HRV		Placebo	
Title	n	s	%	n	s	n	s
Total number of subjects in the primary study (Finland)	2890		100				
Total number of subjects in the Year 3 follow-up	1613			1082		531	
Administration of vaccine(s) forbidden in the protocol (code 1040)	18	18		13	13	5	5
Study vaccine dose not administered according to protocol (code 1070)	4	4		2	2	2	2
Initially positive or unknown status for serum anti-rotavirus IgA antibodies on the day of dose 1 (code 1500)	2	2		0	0	2	2
At least one study vaccine dose not administered (code 3010)	25	25		18	18	7	7
Positive Rotavirus (other than vaccine strain) in stool collected from Dose 1 up to 2 weeks post Dose 2 (code 3030)	3	3		1	1	2	2
Subjects who did not enter into the surveillance period of the second efficacy follow-up period (code 4020)	14	31		9	20	5	11
Subjects not entered the surveillance period of the long-term follow-up period (code 5020)	1234	1277		810	836	424	441
ATP cohort for efficacy for Year 3	1590		55.0	1065		525	

Note: Subjects could have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total number of subjects in the primary study (Finland)

5.3. Demographic characteristics

5.3.1. ATP efficacy cohort

Table 7 presents the summary of demographic characteristics (ATP cohort for efficacy for the follow-up period). Supplement 2 presents the summary of demographic characteristics (Total cohort).

The mean age of subjects at the beginning of this 6-month follow-up study was 31.2 months in the HRV vaccine group (range: 28-35 months) and 31.3 months in the placebo group (range: 28-36 months), respectively. Majority of the subjects were of White-Caucasian or of European heritage (99.6% in the HRV vaccine group and 100% in the

placebo group). Females constituted 46.9% of the subjects in the HRV vaccine group and 50.3% of the subjects in the placebo group.

Table 7 Summary of demographic characteristics (ATP cohort for efficacy for the long-term follow-up period)

		HRV N = 1065		Placebo N = 525		Total N = 1590	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (months)	Mean	31.2	-	31.3	-	31.3	-
	SD	1.11	-	1.19	-	1.14	-
	Median	31.0	-	31.0	-	31.0	-
	Minimum	28	-	28	-	28	-
	Maximum	35	-	36	-	36	-
Gender	Female	500	46.9	264	50.3	764	48.1
	Male	565	53.1	261	49.7	826	51.9
Ethnic	American Hispanic or Latino	0	0.0	0	0.0	0	0.0
	Not American Hispanic or Latino	1065	100.0	525	100.0	1590	100.0
Race	African heritage / African American	0	0.0	0	0.0	0	0.0
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0
	Asian - central/South Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - South East Asian heritage	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific Islande	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	2	0.2	0	0.0	2	0.1
	White - Caucasian / European heritage	1061	99.6	525	100.0	1586	99.7
	Other	2	0.2	0	0.0	2	0.1

N = total number of subjects
n (%) = number (percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Other = In the eCRF, for one subject Race was coded as Arabic and Caucasian/European and for one subject Race was coded as Mother white and father black

6. EFFICACY RESULTS

6.1. Data sets analysed

The analyses of efficacy were performed on the ATP cohort for efficacy (primary analysis). See Section 4.11.4 for the definition of the cohorts identified for analyses and Section 5.2 for eligibility for analyses.

6.2. According-to-protocol analysis

The ATP cohort for efficacy included 1590 subjects (1065 subjects in the HRV vaccine group and 525 subjects in the placebo group).

6.2.1. Characterisation of GE episodes

Table 8 presents the percentage of subjects who reported GE episodes and RV GE episodes during the long-term follow-up period. Table 9 presents the number of GE episodes and RV GE episodes reported during the long-term follow-up period, by severity using the 20-point Vesikari scale. Table 10 presents the number of RV GE episodes reported during the long-term follow-up period by G type.

Supplement 4 presents the percentage of GE episodes with no available stool results during the l term follow-up period (ATP cohort for efficacy). Supplement 5 presents the percentage of subjects with RV GE episodes reported during the long-term follow-up period by G type (ATP Cohort for efficacy). Supplement 6 presents the characteristics (based on Vesikari scale) of RV GE episodes reported during the long-term follow-up period, overall. Supplement 7 presents the distribution of RV GE episodes by the Vesikari score.

Supplement 8 to Supplement 10 present the characteristics of RV GE episodes by isolated RV types.

- During the long-term follow-up period (mean duration: 4.68 months in each group, Supplement 3), 72 (100%) GE episodes were reported by 72 (6.8%) subjects in HRV vaccine group and 36 (100%) GE episodes were reported by 35 (6.7%) subjects in the placebo group.
- Of the stool samples of GE episodes tested, RV was detected in 4 (100%) GE episodes from the HRV vaccine group and in 3 (100%) GE episodes from the placebo group. No subject in either group had more than one episode of RV GE during this long-term follow-up at year 3 (Table 8 and Table 9).
- When the RV GE episodes were scored using the 20-point Vesikari scale, one (25%) RV GE episode in the HRV vaccine group and one (33.3%) RV GE episode in the placebo group were rated as severe (Vesikari score ≥ 11 points) (Table 9).
- Among the circulating RV GE types:
  - A total of three (75%) subjects in the HRV vaccine group reported RV GE episodes caused by the G2 type. One (25%) subject in the HRV vaccine group reported an RV GE episode caused by the G9 type.
  - A total of two (66.7%) subjects in the placebo group reported RV GE episodes caused by the G1 type and one (33.7%) subject reported an RV GE episode caused by the G2 type.
- Stool analysis results were available for 66 of 72 GE episodes (91.6%) in the HRV vaccine group and 33 of 36 GE episodes (91.6%) in the placebo group. No stool

analysis results were available for 9 (8.3%) GE episodes 6 (8.3%) in the HRV vaccine group and 3 (8.3%) GE episodes in the placebo group) as no stool samples were collected during these GE episodes (Supplement 4).

Table 8 Percentage of subjects who reported GE episodes and RV GE episodes during the long-term follow-up period (ATP cohort for efficacy)

Event	Total number of episodes reported	HRV N = 1065		Placebo N = 525	
		n	%	n	%
GE	1	72	6.8	34	6.5
	2	0	0.0	1	0.2
	Any	72	6.8	35	6.7
RV GE	1	4	0.4	3	0.6

N = number of subjects included in each group, for the considered efficacy long-term follow-up period
n (%) = number (percentage) of subjects reporting the specified total number of episode in the considered efficacy period
Any = number and percentage of subjects reporting at least one specified episode in the considered efficacy period

Table 9 Number of GE episodes and RV GE episodes reported during the long-term follow-up period, by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

Event		HRV		Placebo	
	Severity using the 20- point Vesikari scale	Value or n	%	Value or n	%
GE	Mild (1-6)	35	48.6	20	55.6
	Moderate (7-10)	19	26.4	9	25.0
	Severe (≥11)	15	20.8	6	16.7
	unknown	3	4.2	1	2.8
	Any	72	100	36	100
RV GE	Mild (1-6)	2	50.0	1	33.3
	Moderate (7-10)	1	25.0	1	33.3
	Severe (≥11)	1	25.0	1	33.3
	Any	4	100	3	100

n (%) = number (percentage) of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported during the considered efficacy period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy period
unknown = Vesikari severity score = 0

Table 10 Number of RV GE episodes reported during the long-term follow-up period by G type– ATP Cohort for efficacy

	HRV N' = 4		Placebo N' = 3		Total N' = 7	
Characteristics	Value or n	%	Value or n	%	Value or n	%
G1	0	0.0	2	66.7	2	28.6
G2	3	75.0	1	33.3	4	57.1
G9	1	25.0	0	0.0	1	14.3

N'= number of RV GE episodes reported in the considered efficacy period
n (%) = number (percentage) of RV GE episodes reported in the considered efficacy period, by type

6.2.2. Vaccine efficacy against any RV GE (Primary endpoint)

Table 11 presents the percentage of subjects reporting any RV GE and efficacy of the HRV vaccine during the long-term follow-up period.

- Four (0.4%) subjects in the HRV vaccine group and 3 (0.6%) subjects in the placebo group reported any RV GE during the long-term follow-up period (p-value 0.691).VE against any RV GE was 34.3% (95% CI: -348.7.6%; 88.9%).

Table 11 Percentage of subjects reporting any RV GE and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	1065	4	0.4	0.1	1.0	34.3	-348.7	88.9	0.691
Placebo	525	3	0.6	0.1	1.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in the considered efficacy period
% = percentage of subjects reporting at least one RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

6.2.3. Vaccine efficacy against severe RV GE (Secondary endpoint)

Table 12 presents the percentage of subjects reporting a severe RV GE episode (with a score ≥11 in using the 20 point Vesikari scale) and efficacy of vaccine during the long-term follow-up period (ATP cohort of efficacy).

Supplement 11 presents the percentage of subjects reporting severe RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy). Supplement 12 presents the efficacy of the vaccine against severe RV GE with a score ≥ X on the Vesikari scale during the long-term follow-up period (ATP cohort for efficacy).

- One (0.1%) subject in the HRV vaccine group and one (0.2%) subject in the placebo group reported severe RV GE (p-value 0.551). VE against severe RV GE was 50.7% (95% CI: -3769.6%; 99.4%).

Table 12 Percentage of subjects reporting severe RV GE episode (with a score greater than or equal to 11 in using the 20 point Vesikari scale) and efficacy of vaccine during the long-term follow-up period - ATP cohort of efficacy

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	1065	1	0.1	0.0	0.5	50.7	-3769.6	99.4	0.551
Placebo	525	1	0.2	0.0	1.1	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in the considered efficacy period
% = percentage of subjects reporting at least one severe RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

6.2.4. Vaccine efficacy against circulating RV types

6.2.4.1. Vaccine efficacy against any RV GE by RV type (Secondary endpoint)

Table 13 presents the percentage of subjects reporting any RV GE episode by G1, Non-G1 (G2 and G9) types during the long-term follow-up period (ATP cohort for efficacy).

- None of the subjects in the HRV vaccine group reported any RV GE, caused by G1 type when compared to 2 (0.4%) episodes of RV GE reported in the placebo group (p-value 0.109). The VE against any RV GE caused by G1 type was 100.0% [95% CI: -162.5; 100.0%].

- Four (0.4%) subjects in the HRV vaccine group and 1 subject (0.2%) in the placebo group reported RV GE episodes, caused by the non-G1 types (G2 and G9).

  – Three (0.3%) subjects in the HRV vaccine group and 1 subject (0.2%) in the placebo group reported RV GE episodes caused by the G2 type (p-value 1.000).

  – One (0.1%) subject in the HRV vaccine group reported an RV GE episode caused by the G9 type. None of the subjects in the placebo group reported an RV GE episode caused by the G9 type (p-value 1.000) (Table 13).

Table 13 Percentage of subjects reporting any RV GE episode by G1, Non-G1, G2 and G9 types and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy).

RV type	Group	N	n	n/N			VE			p-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
G1 type	HRV	1065	0	0.0	0.0	0.3	100.0	-162.5	100.0	0.109
	Placebo	525	2	0.4	0.0	1.4	-	-	-	-
Non-G1 type	HRV	1065	4	0.4	0.1	1.0	-97.2	-9610.8	80.5	1.000
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
G2 type	HRV	1065	3	0.3	0.1	0.8	-47.9	-7663.7	88.1	1.000
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
G9 type	HRV	1065	1	0.1	0.0	0.5	.	.	98.7	1.000
	placebo	525	0	0.0	0.0	0.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in the considered efficacy period
% = percentage of subjects reporting at least one RV GE episode in the considered efficacy period
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

6.2.4.2. Vaccine efficacy against severe RV GE by RV type (secondary endpoint)

Table 14 presents the percentage of subjects reporting severe RV GE episodes with a score ≥ 11 points on the Vesikari scale by G1, Non-G1 (G2 and G9) types (ATP cohort for efficacy).

- None of the subjects in the HRV vaccine group reported severe RV GE episodes caused by G1 type when compared to one (0.2%) subject reporting a severe RV GE episode in the placebo group (p-value 0.330). The VE against severe RV GE caused by G1 type was 100.0% [95% CI: -1822.5%; 100.0%].
- One (0.1%) subject in the HRV vaccine group reported severe RV GE caused by the non-G1 (G2) type. None of the subjects in the placebo group reported severe RV GE caused the non-G1 (G2) type (p-value 1.000).

Table 14 Percentage of subjects reporting severe RV GE episodes (with a score greater than or equal to 11 in using the Vesikari scale) by G1, non-G1 (G2) types during the long-term follow-up (ATP cohort for efficacy)

RV type	Group	N	n	n/N			VE			p-value
				%	95% CI		%	95% CI		
					LL	UL		LL	UL	
G1 type	HRV	1065	0	0.0	0.0	0.3	100.0	-1822.5	100.0	0.330
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
Non-G1 type	HRV	1065	1	0.1	0.0	0.5	.	.	98.7	1.000
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
G2 type	HRV	1065	1	0.1	0.0	0.5	.	.	98.7	1.000
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one severe RV GE episode with a score ≥11 on the Vesikari scale, in each group
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

6.2.4.3. Vaccine efficacy against RV GE that required medical attention

Table 15 presents the percentage of subjects reporting RV GE episodes that required medical attention and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy).

- One (0.1%) subject in the HRV vaccine group and two (0.4%) subjects in the placebo group reported RV GE episodes that required medical attention (p-value 0.255). The VE against RV GE that required medical attention was 75.4% [95% CI: -373.5%; 99.6%].

Table 15 Percentage of subjects reporting RV GE episode with medical attention and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	1065	1	0.1	0.0	0.5	75.4	-373.5	99.6	0.255
Placebo	525	2	0.4	0.0	1.4	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage) of subjects who sought for medical advice due to RV GE episode
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

6.2.4.4. Vaccine efficacy against all cause severe GE

Table 16 presents the percentage of subjects reporting all cause severe GE episodes and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy).

- A total of 15 (1.4%) subjects in the HRV vaccine group and 6 (1.1%) subjects in the placebo group reported severe GE due to all cause (p-value 0.817).

Table 16 Percentage of subjects reporting all cause severe GE episodes and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	p-value
HRV	1065	15	1.4	0.8	2.3	-23.2	-287.7	54.8	0.817
Placebo	525	6	1.1	0.4	2.5	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting severe GE episode
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

6.2.5. Vaccine efficacy against RV GE scored using the Clark scale

Supplement 13 presents the number of GE episodes and RV GE episodes reported during the long-term follow-up period, by severity using the 24-point Clark scale (ATP cohort for efficacy). Supplement 14 presents the distribution of Clark score for RV GE episodes (ATP cohort for efficacy).

Supplement 15 presents the overall characteristics (based on Clark scale) of RV GE episodes reported during the long-term follow-up period (ATP cohort for efficacy). Supplement 16 to Supplement 18 presents the characteristics (based on Clark scale) of RV GE episodes reported during the long-term follow-up period, by RV types (ATP cohort for efficacy).

- When the RV GE episodes were scored using the Clark scale no subjects reported severe RV GE episodes with a score ≥ 17 on the 24 point Clark scale.
- Comparing the Vesikari and Clark scales, no subjects reported severe RV GE (score >16 points) on the Clark's scale when compared to 2 subjects (1 (0.1%) subject in the HRV vaccine group and 1 (0.2%) subject in the placebo group) reporting severe RV GE (score >11 points) on the Vesikari scale (Supplement 13).

6.3. Total vaccinated cohort analysis

No efficacy analysis was planned on the TVC in the protocol.

7. SAFETY RESULTS

7.1. Data sets analysed

The analysis of safety was performed on the Total cohort (primary analysis) See Section 4.11.4 for the definition of the cohorts identified for analyses and Section 5.2 for eligibility for analyses.

7.2. Total vaccinated cohort analysis

7.3. Serious adverse events

The serious adverse event (SAE) Summary Table(s) is provided in Section 12.1 and the SAE Council for International Organisations of Medical Sciences (CIOMS) are in Section 12.2.

7.3.1. Fatal events

- No fatal events were reported from the end of the second efficacy follow-up period up to the start of this long-term follow-up study.

7.3.2. Non-fatal events

Section 12.1 presents the summary of SAEs reported during the long-term follow-up period.

- During the long-term follow-up period of this study:
  - [redacted] Since the stool sample was not collected for this episode, the episode was not considered for the analysis of RVGE. [redacted] The subject reported vomiting but no diarrhea. Hence this episode was not considered in the GE analysis for any etiology.
  - Pneumonia was reported by two subjects in the placebo group.
  - None of the SAEs reported were considered by the investigator to be causally related to vaccination by the investigator (Section 12.1).

Supplement 19 presents the number of GE episodes from the end of the second year follow-up period of the primary study up to the start of this study (Total cohort).

- The percentage of subjects reporting GE from the end of the second efficacy follow-up period up to the start of this long term follow-up study tended to be lower in the HRV vaccine group when compared to the placebo group (9.5% in the HRV vaccine group and 11.7% in the placebo group) (Supplement 19).
- No IS cases were reported from the end of the second efficacy follow-up period up to the start of this long-term follow-up study.

7.4. Adverse events leading to premature discontinuation of study vaccine and/or study

No AE's leading to withdrawal were reported during the long-term follow-up period of this study.

7.5. Concomitant medications /vaccinations

Not applicable for this long-term follow-up study.

7.6. Clinical laboratory evaluations

Not applicable.

8. DISCUSSION AND OVERALL CONCLUSIONS

8.1. Discussion

The primary study of Rota-036 was conducted in 6 countries (Czech Republic, Finland, France, Germany, Italy and Spain) of Europe to evaluate the efficacy, immunogenicity, reactogenicity and safety of two doses of HRV vaccine in healthy infants. This was followed by a two year efficacy follow-up period during which data collected showed the HRV vaccine to be highly efficacious and causing a significant reduction in the burden of RV GE during the first two years of the infant's life.

Based on these results and the investigators request, the current study was conducted to continue evaluation of the HRV vaccine during the third RV season when the subjects were of 3 years of age. The study was conducted in Finland and included only subjects from the Finnish cohort of the primary study. Finnish subjects who completed the last visit of the year 2 efficacy follow-up period of the primary study, were enrolled.

Since the evaluation of the HRV vaccine during the third RV season was not planned at the start of the primary study there was a delay in the start of this third year follow-up study and the study started only 6 months after the end of the primary study. Owing to the late start many subjects from the Finnish cohort of the primary study were lost to follow-up and subject recruitment was low (1613 subjects in this study as opposed to 2890 subjects in the Finnish cohort of the primary study). Also a delay in study start resulted in the study being conducted during the end of the RV season in Finland when the RV prevalence was low.

The results showed that during the third RV season four (0.4%) subjects in the HRV vaccine group and three (0.6%) subjects in the placebo group reported any RV GE and 1 subject each in the HRV vaccine group and placebo group (0.1% and 0.2%, in the HRV vaccine group and placebo group, respectively) reported severe RV GE.

Among the circulating RV GE types, G2 type was the most prevalent with three (75%) subjects in the HRV vaccine group reporting RV GE episodes caused by the G2 type followed by the G9 type with one (25%) subject reporting an RV GE episode caused by the G9 type. In the placebo group G1 type was the most prevalent with two (66.7%) subjects reporting RV GE episodes caused by the G1 type followed by the G2 type which was isolated from one RV GE episode and reported by one (33.7%) subject.

None of the subjects in the HRV vaccine group reported severe RV GE episodes caused by G1 type. One (0.1%) subject in the HRV vaccine group reported severe RV GE caused by the G2 type. In the placebo group one (0.2%) subject reported a severe RV GE episode caused by G1 type (p-value 0.330). None of the subjects in the placebo group reported severe RV GE caused the G2 type (p-value 1.000). The very low number of RV GE episodes reported in both groups is in line with HRV season of 2006-2007 which was extremely poor as confirmed by the results of the local epidemology study EPI-RV-109547, Finland (study report not available as yet but according to the communication by Prof. [redacted] Also due to the low incidence of RV GE, VE cannot be assessed based on these results.

One (0.1%) subject in the HRV vaccine group and two (0.4%) subjects in the placebo group reported RV GE episodes that required medical attention. All cause severe GE was reported by a total of 15 (1.4%) subjects in the HRV vaccine group and 6 (1.1%) subjects in the placebo group (p-value 0.817).

The current study also had secondary safety objectives to assess the safety of GSK Biologicals' HRV vaccine in terms of mortality, occurrence of IS and occurrence of serious adverse events (SAEs).

Among the SAEs reported during the long-term follow-up period of this study gastroenteritis was reported by one subject each in the HRV vaccine group and the placebo group. None of the SAEs reported were considered by the investigator to be causally related to vaccination. No fatal events were reported from the end of the second efficacy follow-up period of the primary study up to the end of the third RV season. No IS cases were also reported from the end of the second efficacy follow-up period of the primary study up to the start of this long term follow-up study.

8.2. Overall conclusions

- Due to the low number of RV GE cases reported in both HRV vaccine group and placebo group, the vaccine efficacy cannot be assessed from the results of this study.

- Among the circulating RV GE types:
  - A total of three (75%) subjects in the HRV vaccine group reported RV GE episodes caused by the G2 type. One (25%) subject in the HRV vaccine group reported an RV GE episode caused by the G9 type.
  - A total of two (66.7%) subjects in the placebo group reported RV GE episodes caused by the G1 type and one (33.7%) subject reported an RV GE episode caused by the G2 type.
- Among the SAEs reported during the long-term follow-up period, GE was reported by two subjects (one subject each in the HRV vaccine and placebo groups).
- None of the SAEs reported during the long-term follow-up period were considered by the investigator to be causally related to vaccination and all SAEs reported were resolved.

- No IS cases or fatal events were reported from the end of the second efficacy follow-up period up to the start of this long-term follow-up study.
- No clinical concerns can be raised based on the available safety data.

9. SUPPLEMENTS

Supplement 1 Number of subjects by centre (Total cohort)

	HRV	Placebo	Total	
Centre No.	n	n	n	%
[redacted]	129	60	189	11.7
	104	44	148	9.2
	76	36	112	6.9
	40	20	60	3.7
	102	46	148	9.2
	64	32	96	6.0
	53	35	88	5.5
	51	26	77	4.8
	50	21	71	4.4
	48	24	72	4.5
	54	26	80	5.0
	73	34	107	6.6
	39	24	63	3.9
	55	27	82	5.1
	35	17	52	3.2
	42	19	61	3.8
	67	40	107	6.6
All	1082	531	1613	100

n = number of subjects included in each group or in total for a given centre or for all centres
All = sum of all subjects in each group or in total (sum of all groups)
% = n/All x 100
Centre No. = GSK Biologicals assigned centre number

Supplement 2 Summary of demographic characteristics (Total cohort)

		HRV N = 1082		Placebo N = 531		Total N = 1613	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (months)	Mean	31.2	-	31.3	-	31.3	-
	SD	1.12	-	1.19	-	1.14	-
	Median	31.0	-	31.0	-	31.0	-
	Minimum	28	-	28	-	28	-
	Maximum	35	-	36	-	36	-
Gender	Female	510	47.1	266	50.1	776	48.1
	Male	572	52.9	265	49.9	837	51.9
Ethnic	American Hispanic or Latino	0	0.0	0	0.0	0	0.0
	Not American Hispanic or Latino	1082	100.0	531	100.0	1613	100.0
Race	African heritage / African American	0	0.0	0	0.0	0	0.0
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0
	Asian - central/South Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0
	Asian - South East Asian heritage	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific islander	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	3	0.3	0	0.0	3	0.2
	White - Caucasian / European heritage	1077	99.5	531	100.0	1608	99.7
	Other	2	0.2	0	0.0	2	0.1

N = total number of subjects
n (%) = number (percentage) of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Other = In the eCRF, for one subject Race was coded as Arabic and Caucasian/European and for one subject Race was coded as Mother white and father black

Supplement 3 Duration (in years) of the efficacy period (ATP cohort for efficacy)

Duration (years) of long-term follow-up period	HRV N = 1065	Placebo N = 525
Sum	412.4	204.0
Mean	0.39	0.39
SD	0.06	0.06
Minimum	0.11	0.08
Q1	0.36	0.36
Median	0.41	0.41
Q3	0.44	0.44
Maximum	0.48	0.47

N= Number of subjects included in each group in the considered efficacy period
Sum = sum of long-term follow-up period expressed in year for the considered efficacy period
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 4 Percentage of GE episodes with no available stool results during the long-term follow-up period (ATP cohort for efficacy)

Category	HRV N=72		Placebo N=36		Total N = 108	
	n	%	n	%	n	%
No stool results available	6	8.3	3	8.3	9	8.3
No stools collected	6	8.3	3	8.3	9	8.3
Stools collected but no results available	0	0.0	0	0.0	0	0.0

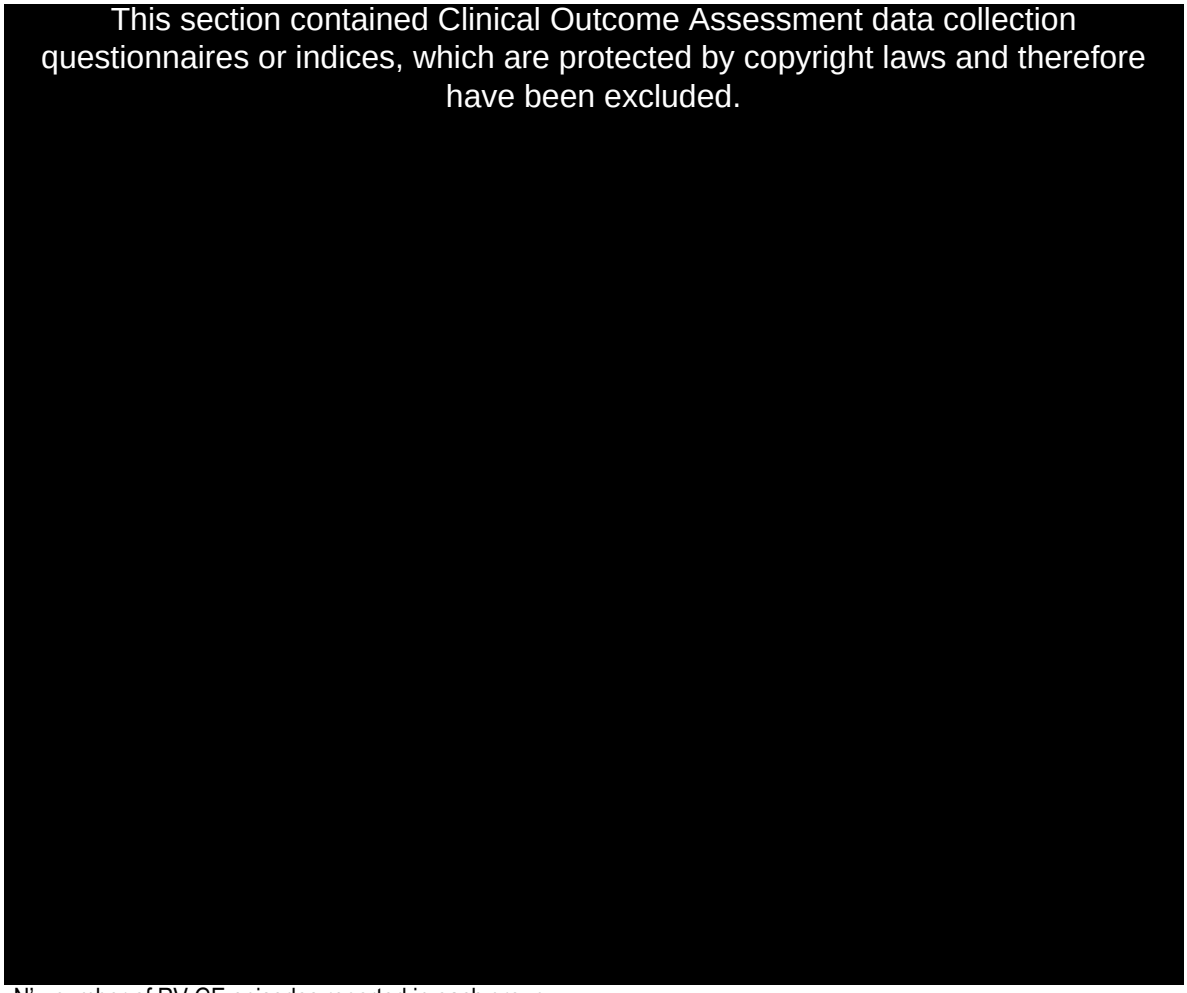
N = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 5 Percentage of subjects with RV GE episodes reported during the long-term follow-up period by G type (ATP Cohort for efficacy)

	HRV N = 1065		Placebo N = 525		Total N = 1590	
Characteristics	Value or n	%	Value or n	%	Value or n	%
G1	0	0.0	2	0.4	2	0.1
G2	3	0.3	1	0.2	4	0.3
G9	1	0.1	0	0.0	1	0.1

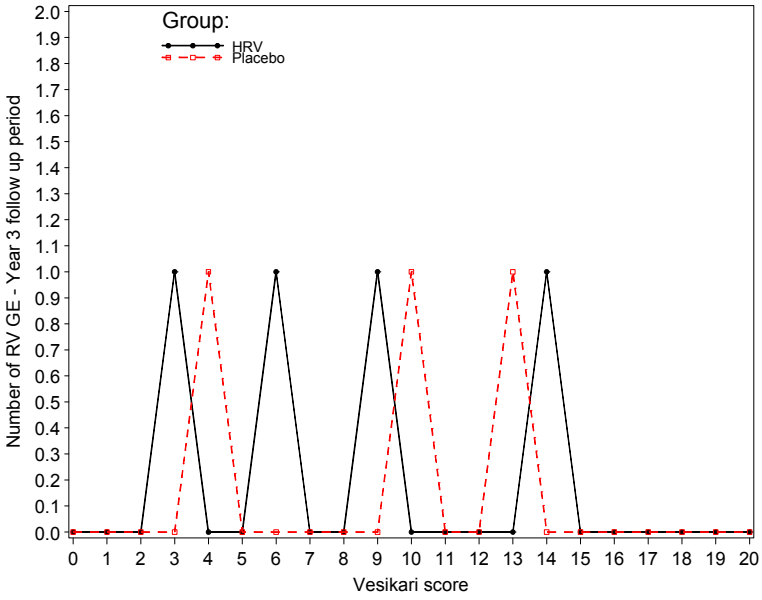
N = number of subjects included in each group, for the considered efficacy period
n (%) = number (percentage) of subjects reporting at least once the specified type in the considered efficacy period

Supplement 6 Characteristics (based on Vesikari scale) of RV GE episodes reported during the long-term follow-up period, overall (ATP cohort for efficacy)



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 7 Distribution of RV GE episodes by the Vesikari score for (ATP cohort for efficacy)



Supplement 8 Characteristics (based on Vesikari scale) of RV GE episodes reported during the long-term follow-up period, by G1 type (ATP cohort for efficacy)

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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 (based on Vesikari scale) of RV GE episodes reported during the long-term follow-up period, by G2 type (ATP cohort for efficacy)

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 Characteristics (based on Vesikari scale) of RV GE episodes reported during the long-term follow-up period, by G9 type (ATP cohort for efficacy)

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

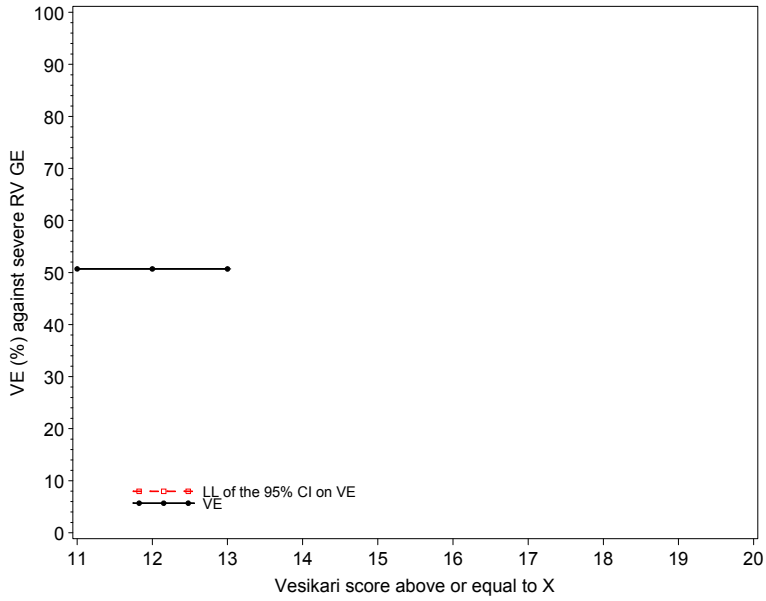
N'= number of RV GE episodes reported in each group
n (%) = number (percentage) of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation

Supplement 11 Percentage of subjects reporting severe RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine during the long-term follow-up period (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	p-value
≥12	HRV	1065	1	0.1	0.0	0.5	50.7	-3769.6	99.4	0.551
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
≥13	HRV	1065	1	0.1	0.0	0.5	50.7	-3769.6	99.4	0.551
	Placebo	525	1	0.2	0.0	1.1	-	-	-	-
≥14	HRV	1065	1	0.1	0.0	0.5	.	.	98.7	1.000
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
≥15	HRV	1065	0	0	0.0	0.3		.	.	.
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
≥16	HRV	1065	0	0	0.0	0.3		.	.	.
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
≥17	HRV	1065	0	0.0	0.0	0.3	.	.	.	-
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
≥18	HRV	1065	0	0.0	0.0	0.3	.	.	.	-
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
≥19	HRV	1065	0	0.0	0.0	0.3	.	.	.	-
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-
≥20	HRV	1065	0	0.0	0.0	0.3	.	.	.	-
	Placebo	525	0	0.0	0.0	0.7	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one severe RV GE episode with a score ≥X [X: 11-20 points] on the Vesikari scale, in each group
LL, UL = 95 % Lower and Upper confidence limits
p value = Two-sided Fisher Exact test

Supplement 12 Efficacy of the vaccine against severe RV GE with a score ≥ X on the Vesikari scale during the long-term follow-up period (ATP cohort for efficacy)

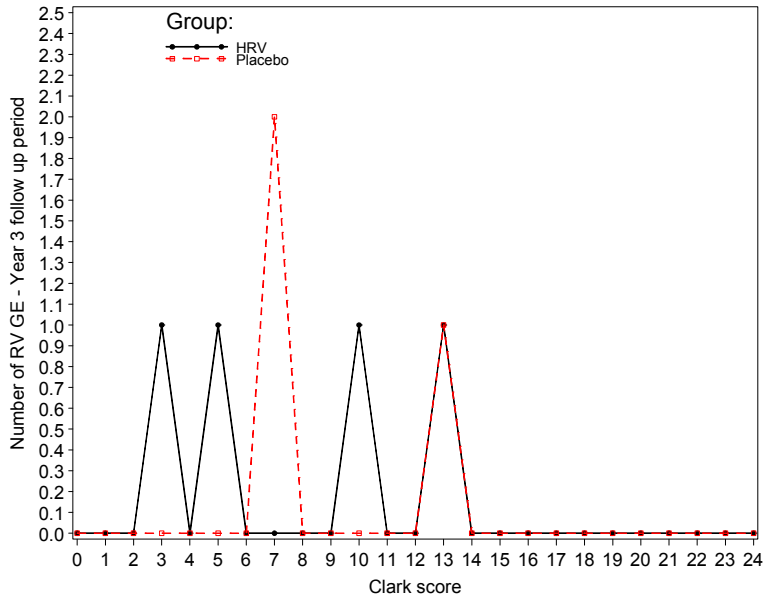


Supplement 13 Number of GE episodes and RV GE episodes reported during the long-term follow-up period, by severity using the 24-point Clark scale (ATP cohort for efficacy)

Event	Severity using the 24- point Clark scale	HRV		Placebo	
		Value or n	%	Value or n	%
GE	Mild (1-8)	49	68.1	27	75.0
	Moderate(9-16)	18	25.0	7	19.4
	unknown	5	6.9	2	5.6
	Any	72	100	36	100
RV GE	Mild (1-8)	2	50.0	2	66.7
	Moderate(9-16)	2	50.0	1	33.3
	Any	4	100	3	100

n (%) = number (percentage) of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported
Any = any specified symptom reported, regardless of Clark severity scale
unkown = Clark's severity score = 0 on the 24 point Clarks scale.

Supplement 14 Distribution of Clark score for RV GE episodes (ATP cohort for efficacy)



Supplement 15 Characteristics (based on Clark scale) of RV GE episodes reported during the long-term follow-up period, overall (ATP cohort for efficacy)

			HRV N' = 4		Placebo N' = 3		Total N' = 7	
	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Overall	severity score	Mean	7.7	-	9.0	-	8.2	-
		SD	4.51	-	3.46	-	3.86	-
		Minimum	3.0	-	7.0	-	3.0	-
		Median	7.5	-	7.0	-	7.0	-
		Maximum	13.0	-	13.0	-	13.0	-
	Duration of looser than normal stools (days)	1-4 Days	4	100	3	100	7	100
	Maximum number of looser than normal stools/day	2-4	1	25.0	2	66.7	3	42.9
		5-7	2	50.0	1	33.3	3	42.9
		> 7	1	25.0	0	0.0	1	14.3
	Duration of vomiting (days)	< 2 days	3	75.0	2	66.7	5	71.4
		2 days	0	0.0	1	33.3	1	14.3
		3-5 days	1	25.0	0	0.0	1	14.3
	Maximum number of episodes of vomiting/day	0	3	75.0	0	0.0	3	42.9
		1-3	0	0.0	2	66.7	2	28.6
		4-6	0	0.0	1	33.3	1	14.3
		>6	1	25.0	0	0.0	1	14.3
	Duration of fever (days)	0	3	75.0	2	66.7	5	71.4
		1- 2 days	1	25.0	1	33.3	2	28.6
	Maximum fever reported /day (measured rectally)	<38.1 °C	3	75.0	2	66.7	5	71.4
		>38.7 °C	1	25.0	1	33.3	2	28.6
	Duration of behavioural symptom	0	1	25.0	0	0.0	1	14.3
		1 – 2 days	2	50.0	1	33.3	3	42.9
		3-4 days	1	25.0	2	66.7	3	42.9
	Behavioural symptoms	None	1	25.0	0	0.0	1	14.3
		Lethargic/listless	3	75.0	3	100	6	85.7

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

Supplement 16 Characteristics (based on Clark scale) of RV GE episodes reported during the long-term follow-up period, by G1 type (ATP cohort for efficacy)

			HRV N'=0		Placebo N' = 2		Total N' = 2	
	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
G1 type	severity score	Mean	-	-	10.0	-	10.0	-
		SD	-	-	4.24	-	4.24	-
		Minimum	-	-	7.0	-	7.0	-
		Median	-	-	10.0	-	10.0	-
		Maximum	-	-	13.0	-	13.0	-
	Duration of looser than normal stools (days)	1-4 Days	-	-	2	100	2	100
	Maximum number of looser than normal stools/day	2-4	-	-	2	100	2	100
	Duration of vomiting (days)	< 2 days	-	-	1	50.0	1	50.0
		2 days	-	-	1	50.0	1	50.0
	Maximum number of episodes of vomiting/day	1-3	-	-	1	50.0	1	50.0
		4-6	-	-	1	50.0	1	50.0
	Duration of fever (days)	0	-	-	1	50.0	1	50.0
		1- 2 days	-	-	1	50.0	1	50.0
	Maximum fever reported /day (measured rectally)	<38.1 °C	-	-	1	50.0	1	50.0
		>38.7 °C	-	-	1	50.0	1	50.0
	Duration of behavioural symptom	3-4 days	-	-	2	100	2	100
	Behavioural symptoms	Lethargic/listless	-	-	2	100	2	100

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

Supplement 17 Characteristics (based on Clark scale) of RV GE episodes reported during the long-term follow-up period, by G2 type (ATP cohort for efficacy)

			HRV N' = 3		Placebo N' = 1		Total N' = 4	
	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
G2 type	severity score	Mean	9.3	-	7.0	-	8.7	-
		SD	4.04	-	0.00	-	3.50	-
		Minimum	5.0	-	7.0	-	5.0	-
		Median	10.0	-	7.0	-	8.5	-
		Maximum	13.0	-	7.0	-	13.0	-
	Duration of looser than normal stools (days)	1-4 Days	3	100	1	100	4	100
	Maximum number of looser than normal stools/day	2-4	1	33.3	0	0.0	1	25.0
		5-7	1	33.3	1	100	2	50.0
		> 7	1	33.3	0	0.0	1	25.0
	Duration of vomiting (days)	< 2 days	2	66.7	1	100	3	75.0
		3-5 days	1	33.3	0	0.0	1	25.0
	Maximum number of episodes of vomiting/24day	0	2	66.7	0	0.0	2	50.0
		1-3	0	0.0	1	100	1	25.0
		>6	1	33.3	0	0.0	1	25.0
	Duration of fever (days)	0	2	66.7	1	100	3	75.0
		1- 2 days	1	33.3	0	0.0	1	25.0
	Maximum fever reported /day (measured rectally)	<38.1 °C	2	66.7	1	100	3	75.0
		>38.7 °C	1	33.3	0	0.0	1	25.0
	Duration of behavioral symptom	1–2 days	2	66.7	1	100	3	75.0
		3-4 days	1	33.3	0	0.0	1	25.0
	Behavioral symptoms	Lethargic/listless	3	100	1	100	4	100

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

Supplement 18 Characteristics (based on Clark scale) of RV GE episodes reported during the long-term follow-up period, by G9 type (ATP cohort for efficacy)

			HRV N' = 1		Placebo N'=0		Total N' = 1	
	Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
G9 type	severity score	Mean	3.0	-			3.0	-
		SD	0.00	-			0.00	-
		Minimum	3.0	-			3.0	-
		Median	3.0	-			3.0	-
		Maximum	3.0	-			3.0	-
	Duration of looser than normal stools (days)	1-4 Days	1	100			1	100
	Maximum number of looser than normal stools/day	5-7	1	100			1	100
	Duration of vomiting (days)	< 2 days	1	100			1	100
	Maximum number of episodes of vomiting/day	0	1	100			1	100
	Duration of fever (days)	0	1	100			1	100
	Maximum fever reported /day (measured rectally)	<38.1 °C	1	100			1	100
	Duration of behavioral symptom	0	1	100			1	100
	Behavioral symptoms	None	1	100			1	100

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

Supplement 19 Number of GE episodes from the end of the second long-term follow-up period up to the start of the study (Total cohort)

HRV N = 1082				Placebo N = 531				Total N = 1613			
		95% CI				95% CI				95% CI	
n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
103	9.5	7.8	11.4	62	11.7	9.1	14.7	165	10.2	8.8	11.8

N = number of subjects
n = number of subject number in a given category
% = n / Number of subject number with GE x 100
LL, UL for percentage = Exact 95% Lower and Upper confidence limits

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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****.*

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Sponsor information	-
Protocol and protocol amendments.	16.1.1
Sample Case Report form (unique pages only).	16.1.2
List of IECs or IRBs (plus name of committee chair if required by regulatory authority)	16.1.3
Representative written information for patient and sample consent forms.	16.1.3
List of investigators and other important participants in the study	16.1.4
Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study	16.1.4
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable).	16.1.6
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Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Sponsor Information

Refer to the appendix protocol and amendment.

Protocol and Protocol Amendments

CONFIDENTIAL

Sponsor:
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Study vaccine	GlaxoSmithKline (GSK) Biologicals' live attenuated oral human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	ROTA-036 EXT Y3 (109810)
EudraCT number	2006-006552-36
Date of approval	Final: 29 November 2006
Title	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Clinical & Medical Affairs, Rotarix & N/S Europe, Clinical Development Europe Management. • [redacted] Senior Clinical Trials Manager. • [redacted] Clinical Trials Manager. • [redacted] and [redacted] Biometricians. • [redacted] Manager-Biometrician • [redacted] Director, Worldwide Clin Ops-Biometrics • [redacted] Medical Advisor. • [redacted] Lead Manager, Worldwide Clinical Development, Rotavirus Vaccines.
Sponsor signatory approval	[redacted] Medical Director, MEDICAL, Medical Management.
Sponsor signatory:	
Signature:	
	_____
Date:	
	_____

Copyright 2006 the GlaxoSmithKline group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited. CARS Id : **CLIN_200611_2679**/ Version : **1.4,Admin. QC**/ Modify Date : **30/11/2006**

Sponsor Information

eTrack study number and abbreviated title	109810 (ROTA-036 EXT Y3)
EudraCT number	2006-006552-36
Title	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

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5. Study Centres

Multiple sites.
Central, co-ordinating unit:
[redacted]
Finland

Investigator Agreement

eTrack study number and abbreviated title	109810 (ROTA-036 EXT Y3)
EudraCT number	2006-006552-36
Title	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
    - Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
    - Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: _____

_____ _____

Investigator signature **Date**

Synopsis

Title	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.
Indication/Study population	Long-term efficacy and safety follow-up up to three years in subjects previously primed with GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
Rationale	Rotavirus disease is the most common cause of diarrhea and dehydration in young children in both developed and developing countries. This heavy global health burden prompted the development of vaccines against rotavirus illness. GlaxoSmithKline (GSK) Biologicals' therefore aims to develop a safe and efficacious rotavirus vaccine that can be used with routine childhood vaccines to meet this health need. GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. This vaccine has been tested extensively in Phase I, II and III trials and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants. The primary vaccination study (Rota-036; eTrack No 102247) was conducted in six European Union countries with 2890 subjects participating from Finland. A two year efficacy follow-up was carried out and it was seen that the HRV vaccine reduced the overall burden of GE in the first year of life. The overall reactogenicity profile of the HRV vaccine was very mild with no increase in any solicited symptoms including fever, diarrhea and vomiting as compared with the placebo during eight days after each dose. This study will assess the long-term efficacy and safety of the subjects during the third year after priming with GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
Objectives	**Primary** • To assess the efficacy of GSK Biologicals' HRV vaccine with respect to any RV GE episodes caused by the circulating wild-type RV strains during the follow-up period.

Secondary

Secondary efficacy objectives:

The objectives during the study period for the long-term follow-up will be:

- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to severe RV GE caused by the circulating wild-type RV strains.
- To assess if the administration of GSK Biologicals' HRV vaccine can prevent any and severe RV GE caused by the wild-type RV strain of serotype G1.
- To assess if the administration of GSK Biologicals' HRV vaccine can prevent any and severe RV GE due to non-G1 serotypes.
- To assess if the administration of GSK Biologicals' HRV vaccine can prevent severe GE.

Secondary safety objectives:

- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of serious adverse events (SAEs) during the follow-up period.
- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of IS during the period from end of the second follow-up period up to the start of the study (retrospective follow-up).

Study design

- Experimental design: Open, long-term follow-up during the third year of age in subjects who participated in the primary study of Rota-036 (eTrack No. 102247) in Finland. For regulatory reasons, the primary study of Rota-036 was decoded. Hence, this long term follow-up will be an open study.
- Subjects who participated in the second year efficacy follow-up will be followed up for efficacy and safety. A total of 2890 subjects from Finland participated in the primary study. Of these, 2601 subjects are expected to be enrolled in this follow-up study from the two groups as follows:
  - Group HRV vaccine (N= 1734)
  - Group Placebo (N= 867)
- Type of study: efficacy and safety follow-up study of Rota-036.

- Data collection: Remote Data Entry (RDE).
- All Adverse events (AE) leading to drop out will be recorded.
- SAEs will be actively collected by GSK during the follow-up period.
- Any gastroenteritis (GE) episode experienced by the subject during the study period of the long-term follow-up period will be recorded.
- Any gastroenteritis (GE) episode experienced by the subject during the end of the second follow-up period up to the start of the follow-up for the third year (retrospective follow-up) should be reported by the subject's parent/ guardian.
- Any occurrence of mortality or IS during the end of the second follow-up period up to the start of the follow-up for the third year (retrospective follow-up) will be recorded.
- All subjects whose parents/guardians give written informed consent will be followed for a period of six months.
- Duration of the study: All subjects will be followed for a period of six months.

Number of subjects

The target sample size for the evaluation of the primary efficacy endpoint will be approximately 2601 enrolled subjects.

Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

Secondary endpoints

Efficacy endpoints

The endpoints during the study period for the long-term follow-up are as follows:

- Occurrence of severe RV GE caused by the wild-type RV strains during the study period for the long-term follow-up.
- Occurrence of any and severe RV GE caused by the wild-type RV strain of serotype G1.
- Occurrence of any and severe RV GE due to non-G1 serotypes.
- Occurrence of severe GE.

Safety endpoints

- Occurrence of mortality and SAEs during the study period for the long-term follow-up.
- Occurrence of mortality and IS during the period from the end of the second follow-up period up to the start of the study.

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APPENDICES

List of Abbreviations

AE	Adverse event
ATP	According-to-protocol
CI	Confidence Interval
CRA	Clinical Research Associate
CSC	Central Study Co-ordinator
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
GCP	Good Clinical Practice
GE	Gastroenteritis
GSK	GlaxoSmithKline
HRV	Human Rotavirus
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	Intussusception
MedDRA	Medical Dictionary for Regulatory Activities
RIA	RadioImmuno Assay
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WHO	World Health Organisation

Glossary of Terms

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Central Study Co-ordinator:	An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring proper conduct of a clinical study.
Diarrhea:	Passage of three or more looser than normal stools within a day.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's clinical trials tracking tool
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 4.4 and 10.3 for details on criteria for evaluability).
Gastroenteritis:	Diarrhea with or without vomiting. Two occurrences of diarrhoea should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.

IDMC:	Independent Data Monitoring Committee. The IDMC is responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Rotavirus gastroenteritis for efficacy analysis:	An episode of GE occurring during the follow-up period in which RV other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of GE symptoms.
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with a score of 11 on a 20-point scoring system (Vesikari scoring system).
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Study Monitor:	An individual assigned by the sponsor who is responsible

	for assuring proper conduct of a clinical study.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Unsolicited adverse event:	Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any "solicited" symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1. INTRODUCTION

1.1. Background

Rotavirus (RV) is the most important cause of acute gastroenteritis (GE) requiring hospitalization of infants and young children in developed and developing countries. Almost all children are infected with rotavirus during early childhood and a large majority of children experience at least one episode of RV Diarrhoea by the age of 24 months. A recent review estimates that 611,000 (range 454,000–705,000) RV-related deaths occur in children less than 5 years of age annually [Parashar, 2006]. The majority of these deaths occur in Africa, Indian subcontinent and Latin America. Epidemiologic studies have shown that the estimated RV disease burden in different European countries is high [Vesikari, 1999; Koopmans, 1999; Mrukowicz, 1999; Johansen, 1999] and most of this burden is due to RV-associated hospitalization of young children. In Europe, the estimated RV associated hospitalization rates among children under 5 years of age vary from 1 in 33 cases of RV infection in Finland, 1 in 54 in Sweden, 1 in 65 in Poland, 1 in 74 in the Netherlands and 1 in 80 in Spain [Gil, 2004].

The significant global health burden due to RV disease in both developed and developing countries prompted the development of RV vaccines. Prevention by vaccination is considered to be critical for effective control of RV infection since only non-specific symptomatic therapies are available. A variety of approaches to the development of RV vaccines have been undertaken, with live oral attenuated vaccines receiving the most attention. One vaccine, Rotashield®, a tetravalent rhesus human reassortant RV vaccine (RRV-TV), was licensed by Wyeth-Lederle in the United States in 1998 and was granted a marketing authorization for Europe in 1999 but was withdrawn from the market in 1999 due to an increased risk of intussusception (IS) (telescoping of the intestine) shortly after its administration. GlaxoSmithKline (GSK) Biologicals therefore aims to develop a safe and efficacious human rotavirus vaccine to meet this health need. GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old infant with a mild RV diarrhea in Cincinnati, United States. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilized HRV vaccine containing RIX4414 cloned from 89-12 at passage 43 for oral administration after reconstitution with buffer. The parent 89-12 vaccine was well-tolerated, immunogenic and effective in preventing RV GE among vaccinated infants during a trial in the United States [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002].

GSK's RIX4414 candidate HRV differs from Rotashield®, because it is based on a human strain, whereas Rotashield® was based on a rhesus strain. There are major differences in terms of biological properties and clinical symptoms between animal (rhesus) and human RV strains, while only minor differences are expected between the attenuated RIX4414 HRV strain and the wild-type HRV. Wild-type HRV has not been associated with IS in infants. The most powerful evidence refuting a link between wild type HRV infection and IS is the absence of an increase in IS rates during the sharply defined winter RV epidemics that occur in temperate climates [Rennels, 1998]. The

RIX4414 human strain in GSK Biologicals' candidate HRV vaccine is attenuated and the attenuation might further decrease any possible, albeit unlikely, link to IS. Administration of GSK's HRV vaccine candidate does not induce a viral exposure that would otherwise not occur, in contrast with the administration of the rhesus rotavirus vaccine which represents a virus that would not normally infect children.

Clinical results of the GSK Biologicals HRV vaccine

GSK Biologicals' HRV vaccine has been tested in Phase I-III clinical studies and shown to be immunogenic, efficacious, safe and well-tolerated with only mild side effects in adults, previously infected children (1-3 years old) and infants.

Safety

As of 15 July 2005, the safety database for GSK Biologicals' HRV vaccine contains 89,243 subjects. Up to 15 July 2005, 5,782 subjects have reported a total of 6,872 SAEs. Of these, a total of 67 SAEs have been considered by the investigators as possibly related or with unknown relationship.

A large phase III multinational trial [GSK Biologicals Clinical Report 444563/023(Rota-023)] involving 63,225 infants was undertaken in 11 countries in Latin America and in Finland with primary safety objective of assessing the safety of the HRV vaccine in terms of occurrence of definite intussusception (IS). The primary safety evaluation was based on occurrence of definite IS during 31 days (Day 0 to Day 30) after each vaccine dose. The rationale for focussing on the critical risk window of 31 days after vaccination was based on the consideration that vaccination-related IS would occur when the vaccine virus replication and host responses are maximal. Thirteen IS cases (6 in the HRV vaccine group and 7 in the placebo group) diagnosed within the 31 days (Day 0 to Day 30) risk window were adjudicated as Definite IS by an independent external expert committee. The primary safety objective of the study was met with the Risk Difference of -0.32/ 10 000 (95%CI: 2.91/ 10 000-2.18/ 10 000) vaccinees and the Relative Risk of 0.85 (95% CI: 0.30-2.42) providing evidence of no increased risk of IS for the HRV vaccine within 31 days after any dose.

Study Rota-023 was also one of the largest efficacy trial for a rotavirus vaccine, with a total of 20,169 vaccinated subjects (10,159 in the HRV vaccine group and 10, 010 in the Placebo group) in the efficacy cohort. The efficacy follow-up visit (Visit 4) at one year of age was completed by 17, 882 subjects (88.7%). Active surveillance was conducted to identify severe GE episodes. Severe GE was defined as a GE episode requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV strains during the period starting from completion of the immunization (2 weeks post Dose 2) until one year of age was 84.7% (95% CI: 71.7%-92.4%) (primary efficacy endpoint). The criteria specified for fulfilling the primary efficacy objective was met. The HRV vaccine was highly effective in protecting against severe RV GE episodes caused by the globally predominant G1 type with a vaccine efficacy of 91.8% (95% CI: 74.1%-98.4%). The HRV vaccine was equally protective against the emerging G9 type, with an efficacy of 90.6% (95% CI: 61.7%-98.9%). The HRV vaccine also provided significant protection against severe RV GE due to the G3 type with efficacy of 87.7% (95% CI:

8.3%-99.7%). A protective trend against G2 type was also observed. A meta analysis of the completed efficacy trials with HRV vaccine [GSK Biologicals Clinical Report 444563/004, GSK Biologicals Clinical Report 444563/006, GSK Biologicals Clinical Report 444563/007, GSK Biologicals Clinical Report 444563/023 and GSK Biologicals Clinical Report 444563/036 showed vaccine efficacy of 71.4% [95% CI: 20.1%; 91.1%] against severe RV GE episodes [Ruuska, 1990] caused by the G2 type. These results provide evidence that this G1P [8] HRV vaccine elicits cross-protection.

An Independent Data Monitoring Committee (IDMC) has been appointed to monitor the safety aspects in all trials during the HRV vaccine clinical development. All reported SAEs unblinded by treatment group are periodically reviewed by the IDMC.

Please refer to the European Summary of Product Characterisation for a review of the clinical studies of Rotarix as the vaccine has been licensed in Finland.

1.2. Rationale for the study

Rotavirus disease is the most common cause of diarrhea and dehydration in young children in both developed and developing countries. This heavy global health burden prompted the development of vaccines against rotavirus illness. GlaxoSmithKline (GSK) Biologicals' therefore aims to develop a safe and efficacious rotavirus vaccine that can be used with routine childhood vaccines to meet this health need.

GSK Biologicals' rotavirus vaccine is a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. This vaccine has been tested extensively in Phase I, II and III trials and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.

The primary vaccination study (Rota-036; eTrack No 102247) was conducted in six European Union countries with 2890 subjects participating from Finland. A two year efficacy follow-up was carried out and it was seen that the HRV vaccine reduced the overall burden of GE in the first year of life. The overall reactogenicity profile of the HRV vaccine was very mild with no increase in any solicited symptoms including fever, diarrhea and vomiting as compared with the placebo during eight days after each dose.

This study will assess the long-term efficacy and safety of the subjects during the third year of age after priming with GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine.

2. OBJECTIVES

2.1. Primary objective

- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to any RV GE episodes caused by the circulating wild-type RV strains during the follow-up period.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

Secondary efficacy objectives:

The objectives during the study period for the long-term follow-up will be:

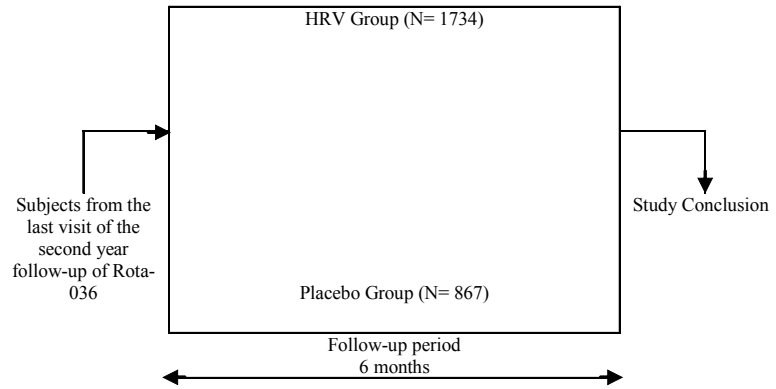
- To assess the efficacy of GSK Biologicals' HRV vaccine with respect to severe RV GE caused by the circulating wild-type RV strains.
- To assess if the administration of GSK Biologicals' HRV vaccine can prevent any and severe RV GE caused by the wild-type RV strain of serotype G1.
- To assess if the administration of GSK Biologicals' HRV vaccine can prevent any and severe RV GE due to non-G1 serotypes.
- To assess if the administration of GSK Biologicals' HRV vaccine can prevent severe GE.

Secondary safety objectives:

- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of serious adverse events (SAEs) during the follow-up period.
- To assess the safety of GSK Biologicals' HRV vaccine in terms of mortality and occurrence of IS during the period from end of the second follow-up period up to the start of the study (retrospective follow-up).

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW



N= No. of subjects planned to be enrolled in the long-term follow-up

- Experimental design: Open, long-term follow-up at approximately three years of age in subjects who participated in the primary study of Rota-036 (eTrack No. 102247) in Finland. For regulatory reasons, the primary study of Rota-036 will be decoded. Hence, this long term follow-up will be an open study.

- Subjects who participated in the second year efficacy follow-up will be followed up for efficacy and safety. A total of 2890 subjects from Finland participated in the primary study. Of these, 2601 subjects are expected to be enrolled in this follow-up study from the two groups as follows:
  - Group HRV vaccine (N= 1734)
  - Group Placebo (N= 867)
- Type of study: efficacy and safety follow-up study of Rota-036.
- Data collection: Remote Data Entry (RDE).
- All Adverse events (AE) leading to drop out will be recorded.
- SAEs will be actively collected by GSK during the follow-up period.
- Any gastroenteritis (GE) episode experienced by the subject during the study period of the long-term follow-up period will be recorded.
- Any gastroenteritis (GE) episode experienced by the subject during the end of the second follow-up period up to the start of the follow-up for the third year (retrospective follow-up) should be reported by the subject's parent/ guardian.
- Any occurrence of mortality or IS during the end of the second follow-up period up to the start of the follow-up for the third year (retrospective follow-up) will be recorded.
- All subjects whose parents/guardians give written informed consent will be followed for a period of six months.
- Duration of the study: All subjects will be followed for a period of six months.

4. STUDY COHORT

4.1. Number of subjects/ centres

At the time of initiation of the study, the investigator will contact ALL subjects who completed the second year efficacy follow-up of the primary vaccination study (eTrack No.102247) from the centres in Finland. If at the time of initiation of the long-term study, any parent/ guardian of the subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.

A total of 2601 subjects are expected to participate in this study.

Refer to Section 10.3 for the estimated sample size.

4.2. Inclusion criteria

All subjects must satisfy the following criteria at study entry:

- A male or female who has completed the second year efficacy follow-up of the primary vaccination study (Rota-036, eTrack No.102247) in Finland.
- Written informed consent obtained from the parent or guardian of the subject.

4.3. Exclusion criteria for enrolment into the long-term follow-up

Not applicable as this study is a long-term efficacy and safety follow-up of subjects who have received the HRV vaccine or the placebo dose in the primary vaccination study (Rota-036).

4.4. Elimination criteria during the study

If any of the elimination criteria become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.3 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the long-term follow-up.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the long-term follow-up. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)
- Administration of immunoglobulins and/or any blood products during the long-term follow-up period.

4.5. Contraindications to subsequent vaccination

Not applicable.

4.6. Warnings and Precautions

Not applicable.

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the October 1996 version of the Declaration of Helsinki (Protocol Appendix A) and local rules and regulations of the country.
Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/ IRB submission or approval and whether or not the authority will provide their approval of or

favourable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

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. The ICH Harmonized Tripartite Guideline for Good Clinical Practice recommends that the IRB/ IEC should include:

a. At least five members.

b. At least one member whose primary area of interest is in a non-scientific area.

c. 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 provide opinion on a study-related matter.

A list of IRB/ IEC members and their qualifications should be obtained by the investigator.A list of the professions of the IRB/ IEC members should be obtained by GSK biologicals' 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 the IRB/ IEC by the investigator. Written and dated unconditional approval/favourable opinion from the IRB/ IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favourable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/ IEC for review and approval of the protocol. Verification of the unconditional approval/favourable opinion of the IRB/ IEC will be transmitted by the investigator to GSK Biologicals' local Study Monitor.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/ IEC approval/ favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].) Administrative changes and amendments not submitted for approval are submitted to the IRB/ IEC for information only. However, written verification that such documents were submitted should be obtained. Approvals/ verifications must be transmitted in writing to GSK Biologicals' Study Monitor by the investigator.

The IRB/ IEC must be informed by the investigator of:

- all subsequent protocol amendments, 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 administrative changes (for information, except for US studies),
- 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.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/ IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

5.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the 1996 version of the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/ IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to the subjects' parents/guardians .

Freely given informed consent should be obtained from every subject's parents/guardians prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/ IEC.

An investigator or designate will describe the protocol to potential subjects' parents/ guardians face to face. The Informed Consent Form may be read to the subjects' parents/ guardians, but, in any event, the investigator or designate shall give the subjects' parents/ guardians ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each subject's parents/ guardians must be given the opportunity to individually pose questions to the investigator or designate prior to the subject's parents/ guardians dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects' 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 parents/

guardians and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the parents'/ guardians' incapacity precludes this and provided that the local legal obligations are fulfilled.

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/ or GSK Biologicals' professional and Regulatory Compliance persons. The parents/ guardians should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects' parents/ guardians, and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects' parents/ guardians.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the subjects' parents/ guardians should include explanations of the following:

a. That the trial involves research.

b. The purpose of the trial.

c. The trial treatment(s) and the probability for random assignment to each treatment.

d. The trial procedures to be followed, including all invasive procedures.

e. The subject's parents'/guardians' responsibilities.

f. Those aspects of the trial that are experimental.

g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.

h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects' parents/guardians should be made aware of this.

i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.

j. The compensation and/or treatment available to subjects in the event of trial-related injury.

k. The anticipated prorated payment, if any, to subjects' parents/guardians for participating in the trial.

l. The anticipated expenses, if any, to subjects' parents/guardians for participating in the trial.

m. That the subjects' participation in the trial is voluntary and subjects' parents/guardians may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.

n. That the monitor(s), the auditor(s), the 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 subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject's parents/guardians is authorizing such access.

o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects' parents/guardians will be informed in a timely manner if information becomes available that may be relevant to the subjects' parents/guardians willingness for continued participation in the trial.

q. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and who to contact in the event of trial-related injury.

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/ IEC and be acceptable to GSK Biologicals.

5.2. General study aspects

5.2.1. Independent Data Monitoring Committee (IDMC)

An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE/ IS case and each case fatality is reviewed unblinded by treatment group by this committee.

5.3. Subject identification

Subject numbers which were assigned sequentially to subjects who participated in the primary vaccination study in multicentres in Finland will be retained for this long-term efficacy and safety follow-up.

5.4. Surveillance of SAEs

Parents/ guardians of all subjects will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious. SAEs will be actively collected by GSK during the follow-up period.

5.5. Follow-up of GE episodes and collection of stool samples

A retrospective follow-up for the occurrence of GE episodes will be conducted where the parents/ guardians will be asked to report any GE episode that might have occurred between the end of the second year efficacy follow-up up to the start of this year three follow-up.

Active follow-up for occurrence of GE episodes will be conducted during the follow-up period. The parents/ guardians will be provided with diary cards to record any GE episode. Each subject's parent/ guardian will be contacted once every two weeks to check on the occurrence of any GE. This contact will be by telephone or short message service (SMS) using cellular phone. In case of unavailability of the subject's parent/ guardian at the time of contact, at least one more attempt will be made before the next planned contact.

For each suspected GE episode occurring during the study period, the GE diary card should be completed by the parents/ guardians daily until end of the GE symptoms (Refer to section 8.11 for details of GE assessments). Information on all medical attention related to this GE episode and therapies used to treat the episode will also be recorded on the same card. Behavioural symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

The completed diary cards will be collected by the study personnel. The parents/ guardians will be reminded to return the diary cards and incase the diary card is illegible or in case of any missing data, telephone contacts will be made to those parents/ guardians. The investigator will verify the returned completed GE diary card and (s)he or study personnel will transcribe the information into the appropriate sections of the eCRF, in English.

For each GE episode occurring during the study period, a stool sample should be obtained from the subject. The stool sample should be collected as soon as possible after symptoms begin but not later than 7 days after the onset of GE symptoms. A stool sample should be collected for each separate diarrhoea episode. A second stool sample should be collected if the first sample is insufficient (based on the discretion of the parent/ guardian). Two occurrences of diarrhoea should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.

The stool sample should be stored in a home freezer until it is transferred rapidly to the investigator's laboratory. The stool sample should be stored frozen at approximately –20°C or colder until shipped to [redacted] laboratory.

5.6. Outline of study procedures

Table 1 presents the outline of study procedures.

Table 1 List of study procedures

	Timing: Beginning of January 2007 up to the end of June 2007
Informed consent	●
Check inclusion criteria at long-term follow-up time point	●
Check elimination criteria	●
Medical history	●
Reporting of all GE since the last visit in the 2nd yr follow up	●
Retrospective collection of cases of IS and mortality since the last visit in the 2nd yr follow-up	●
Collection of stool samples if the child develops GE	●
Reporting of all GE during the follow-up period	●
Reporting of SAEs during the follow-up period	●
Reporting of mortality during the follow-up	●
Reporting of AEs leading to subject withdrawal and drop out	●
Telephone contact or SMS	●
Return of GE diary cards	●
Diary card transcription by investigator	●
Study Conclusion	●

● is used to indicate a study procedure which requires documentation in the eCRF.

It is the investigator's responsibility to ensure that the interval between the previous follow-up (at year two) and the current follow-up visit are followed as closely as possible.

5.7. Detailed description of study stages/visits

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.3 for definition of study cohorts to be evaluated). The investigator must ensure that his/ her personnel and the laboratory(ies) under his/ her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D.

5.7.1. Subjects followed for safety and efficacy

Time period from beginning of January 2007 up to the end of June 2007.

- Informed consent will be obtained from the parent/ guardian through mail prior to the start of the long-term follow-up study. The ICF will be accompanied with a covering letter with instructions on the collection of stool samples in case of the occurrence of any GE episode.
- Checking of inclusion criteria at the time of the third year follow-up.
- Checking of elimination criteria.
- The subject's parent/ guardian will be instructed to report all GE episodes that might have occurred between the end of the second year efficacy follow-up up to the start of this year three follow-up and report all GE episodes that the subject experiences during the study period for the long-term follow-up.
- Collection of any stool samples (in case of any GE episode): Diary cards and material for sample collection will be mailed to the parents/ guardians of all subjects in the long-term follow-up. Parents/ guardians will be instructed to collect the stool samples in plastic bags or tubes provided by the sponsor.. Parents/ guardians will be contacted bi-weekly through a telephone call or short message service. The study personnel will make a home visit and collect the stool sample and the diary card in case of any GE episode. If the GE episode is still ongoing when the study personnel makes the home visit for sample collection, then the diary cards can be mailed to the study centre later.
- The subjects' parents/ guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Collection of the completed GE diary cards. The investigator will verify the completed diary card and transcribe the information into the appropriate sections of the eCRF, in English. The site monitor may help in this translation.
- Transcription of local laboratory results of stool analysis, when available, in the eCRF.
- Recording of any IS that may have occurred since the last visit in the second year follow-up in the eCRF.
- Recording of SAEs and mortality during the study period for the long-term follow-up.
- Study conclusion of the long-term follow-up.

5.8. Sample handling and analysis

5.8.1. Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

5.8.2. Laboratory assays

5.8.2.1. GE stool analysis

Stool samples collected during GE episodes will be processed at the study site and transported to the [redacted]laboratory where further analysis will be carried out for HRV detection using Dako IDEIA EIA Test. (Refer to Appendix E).

If a stool sample tests positive for RV, the sample will be tested by Polymerase Chain Reaction (PCR) in the [redacted]aboratory to determine the serotype. No additional testing will be performed by the investigator without prior GSK Bio approval.

Any additional testing on stool samples will be performed if deemed necessary by GSK Biologicals if any findings in the present study or in other studies necessitate investigation of the vaccine.

5.8.3. Endpoints for suboptimal response

Not applicable.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

Not applicable in this efficacy and safety follow-up study.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

Each subject's parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

In this long-term follow-up for efficacy and safety, the occurrence of any GE episode will be primarily assessed. (Refer to Section 8.11 for details on the assessment of GE).

Section 8.1 applies to subjects withdrawn from the study due to GE and or AE leading to drop out.

8.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/ SAE).

Examples of an AE do not include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AEs may include post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the long-term follow-up study.

8.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. results in death,

b. is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which 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.

c. requires hospitalization or prolongation of existing hospitalization,

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. is a congenital anomaly/birth defect in the offspring of a study subject.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

8.2.1. Disease-related events or outcomes not qualifying as serious adverse events

Not applicable.

8.3. Lack of efficacy

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the AE or SAE definition (including clarifications).

8.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. ECGs, X-rays, vital signs, ultrasound etc.) that are judged by the investigator to be clinically significant will be recorded as SAEs if they meet the definition of a SAE, as defined in Section 8.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study will be reported as SAEs. The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.5. Time period, frequency and method of detecting AEs and serious adverse events

All AEs leading to subject withdrawal must be recorded on the Adverse Event form in the subject eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

Any occurrence of mortality or IS during the end of the second follow-up period up to the start of the follow-up for the third year (retrospective follow-up) will be recorded.

SAEs will be actively collected by GSK during the follow-up period.

The investigator will inquire about the occurrence of SAEs at every contact during the study.

When an AE/ SAE leading to subject withdrawal or drop out occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/ SAE on the eCRF/ SAE Report Form as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed eCRF/ SAE pages. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/ SAE and not the individual signs/symptoms.

8.6. Evaluating adverse events and serious adverse events

8.6.1. Assessment of intensity

Intensity of the AEs leading to subject withdrawal or drop out and SAEs will be assessed as described:

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for all AE and SAEs reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the eCRF or SAE Report Form, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE/ SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE/ SAE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE/ SAE which prevents normal, everyday activities. (In a young child, such an AE/ SAE would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.2.

8.6.2. Assessment of causality

Causality of the AEs leading to subject withdrawal or drop out and SAEs:

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/ SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Product Information, for marketed products, in the determination of his/ her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE Report Form to GSK Biologicals. The investigator may change his/ her opinion of causality in light of follow-up information, amending the SAE Report Form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality of all AE/ SAEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE/ SAE may have been caused by the investigational product?

NO	:	The AE/ SAE is not causally related to administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE/ SAE.
YES	:	There is a reasonable possibility that the vaccine contributed to the AE/ SAE.

Serious AEs will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 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
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine(s), if applicable
- Erroneous administration
- Other cause (specify)
- Death.

8.6.3. Medically attended visits

For each GE episode that the subject experiences, the subject's parents/guardians will be asked if they received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the eCRF.

8.7. Follow-up of adverse events and serious adverse events and assessment of outcome

After the initial AE/ SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous contact and designated as not recovered/ not resolved or recovering/ resolving will be reviewed at the end of the follow-up period.

Investigators will follow-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, the event is otherwise explained, or the subject is lost to follow-up;

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided.

GSK Biologicals may request that the investigator perform or arrange for the conduct of supplemental measurements and/ or evaluations to elucidate as fully as possible the nature and/ or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during the recognized follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE Report Form, with all changes signed and dated by the investigator. The updated SAE report form should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.8.1.

Outcome of any non-serious AE leading to subject withdrawal or any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.8. Prompt reporting of serious adverse events to GSK Biologicals

8.8.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. The investigator or designate will fax the SAE reports to GSK Biologicals' Study Contact for Serious Adverse Event Reporting **WITHIN 24 HOURS OF HIS/ HER BECOMING AWARE OF THESE EVENTS**. Additional or follow-up information relating to the initial SAE report is also to be reported to the GSK Biologicals' Study Contact for Serious Adverse Event Reporting within 24 hours of receipt of such information.

8.8.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, she/ he will report the information to GSK within 24 hours as outlined in Section 8.8.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK Biologicals within the designated time frames. If the investigator does not have all information regarding an SAE, he/ she will not wait to receive additional information before notifying GSK Biologicals of the event and completing the form. The form will be updated when additional information is received and forwarded to GSK **WITHIN 24 HOURS** as outlined in Section 8.8.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.6.2.

Facsimile (Fax) transmission of the SAE Report Form is the preferred method to transmit this information to the Study Contact for Reporting SAEs. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours as outlined in Section 8.8.1.

In the event of a death determined by the investigator to be related to vaccination, sending of the fax must be accompanied by telephone call to the Study Contact for Reporting SAEs.

The standard Verbal Autopsy Questionnaire (see Appendix G) 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 report.

Study Contact for Reporting SAEs
Name, address: [redacted] GlaxoSmithKline PO Box 24 (Piispansilta 9A), 02231 Espoo, Finland Tel: [redacted] Fax: [redacted] (Backup: [redacted] Mobile: : [redacted] Email: [redacted]
Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety Physician Tel: [redacted] Fax: [redacted] or [redacted] Mobile phones for 7/7 day availability: [redacted] Back-up mobile phone contact: [redacted] **24/24 hour and 7/7 day availability**

8.9. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.8. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.10. Post-study AEs and serious adverse events

A post-study AE/ SAE is defined as any event that occurs outside of the AE/ SAE detection period defined in Section 8.5. Investigators are not obligated to actively seek AEs or SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.11. Assessment of GE episodes

The occurrence of any retrospective GE will be recorded.

Any GE episode (defined as diarrhea with or without vomiting) occurring during the study period should be documented using the GE diary card. The following information will be collected on the GE diary card during each GE episode: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be also recorded. The information collected on the GE diary card will allow the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

Medical attention (medical provider contact, advice, visit; emergency room contact or visit or hospitalization) will also be recorded in the diary card for each GE episode.

Behavioural symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

In the 20-point scoring system [Ruuska, 1990], points will be assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalization (hospitalized subjects will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 2.

Table 2 The 20-point scoring system to determine the intensity of GE episodes reported during the study

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

∗ The highest temperature recorded during the episode will be scored.

A score < 7 is prospectively defined as mild, a score 7 - 10 is prospectively defined as moderate and a score ≥ 11 is prospectively defined as severe [Joensuu, 1997].

Periodic contact will be made with the subjects' family to enquire about the occurrence of GE, medical care or advice, and hospitalization. Collection of a stool sample will be requested if not yet provided and if GE occurred since last contact.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject, whose parent / guardian is available for the concluding contact foreseen in the protocol, is considered to have completed the study.

9.2. Subject withdrawal

Subjects who are withdrawn for a SAE/ AE must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/ AE until resolution of the event.

Withdrawals during the study will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study is any subject who did not make the concluding contact foreseen in the protocol.

A subject qualifies as a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subject's parent/ guardian if they are not available at the time of first phone contact.

Information relative to the withdrawal will be documented on the Study Conclusion section of the eCRF. The investigator will document whether the decision to withdraw from the study was made by the subject's parent or guardian or the investigator and which of the following possible reasons was responsible for withdrawal:

- serious adverse event
- non-serious adverse event (specify)
- protocol violation (specify)
- consent withdrawal, not due to an adverse event
- moved from the study area
- lost to follow-up
- other (specify)

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Primary endpoint

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

10.2. Secondary endpoints

Efficacy endpoints

The endpoints during the study period for the long-term follow-up are as follows:

- Occurrence of severe RV GE caused by the wild-type RV strains during the study period for the long-term follow-up
- Occurrence of any and severe RV GE caused by the wild-type RV strain of serotype G1.
- Occurrence of any and severe RV GE due to non-G1 serotypes.
- Occurrence of severe GE.

Safety endpoints

- Occurrence of mortality and SAEs during the study period for the long-term follow-up.
- Occurrence of mortality and IS during the period from the end of the second follow-up period up to the start of the study.

10.3. Estimated sample size

The primary objective of the study is to assess if two doses of GSK Biologicals' HRV vaccine can prevent any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

Subjects from Finland who completed the second year efficacy follow-up of the primary study will be followed up for this study. A total of 2890 subjects from Finland participated in the primary study (Rota-036 (eTrack No. 102247). Assuming that up to 10% of the subjects may not be willing to participate in this study; 2601 subjects are expected to be enrolled in this follow-up study. Allowing for up to 10% of subjects who may not be evaluable for analyses of the primary objective, 2340 subjects (1560 in HRV and 780 in placebo groups respectively) are expected to be evaluable for the analysis of the primary objective.

Considering a 2:1 randomization ratio and various incidence rates, Table 3 provides the power that the 95% CI for vaccine efficacy be above given limits.

Therefore, if the vaccine efficacy is truly 70% and if the incidence rate is 3.5%, the study has at least 80% power to observe that the lower limit of the 95% CI for the vaccine efficacy that will be above 20%.

Table 3 Power to observe a 95% CI above various cut-offs according to various incidence rates and a true vaccine efficacy of 70% (power obtained from simulations using 1560 evaluable subjects in the HRV vaccine group and 780 evaluable subjects in the placebo group)

Incidence rate in the placebo	True vaccine efficacy	Cut-off for the lower limit of the 95% CI on vaccine efficacy			
		0%	10%	20%	30%
Any Gastroenteritis					
3.5%	70%	95%	92%	86%	75%
1%	70%	45%	34%	30%	21%

10.4. Study cohorts to be evaluated

10.4.1. Total cohort

The total cohort will include all subjects who participate in this follow up study with at least one vaccine administration documented in the primary study:

- an efficacy analysis based on the total cohort will include all subjects for whom efficacy follow-up data are available

10.4.2. According-To-Protocol (ATP) cohort for analysis of safety

Not applicable.

10.4.3. ATP cohort for analysis of immunogenicity

Not applicable.

10.4.4. ATP cohort for analysis of efficacy

The ATP cohort for efficacy will include all subjects from the ATP efficacy cohort of the primary study who have entered into the efficacy surveillance period.

10.5. Derived and transformed data

Efficacy

An episode of GE will be classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain is identified in a stool sample collected during the episode. GE episode without stool sample/result available will not be considered in the analysis as a RV GE episode.

10.6. Final analyses

10.6.1. Analysis of demographics/baseline characteristics

The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group.

10.6.2. Analysis of efficacy

Vaccine efficacy will be calculated, with their 95% CI (see Appendix F for mathematical details) against:

- any and severe RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.
- any and severe RV GE due to G1 serotype caused by the circulating wild-type RV strains during the study period for the long-term follow-up.
- any and severe RV GE due to non-G1 serotypes during the study period for the long-term follow-up.
- severe GE during the study period for the long-term follow-up.

Exploratory efficacy analysis based on history of GE in the primary study will be done.

10.6.3. Analysis of immunogenicity

Not applicable.

10.6.4. Analysis of safety

Serious adverse events and mortalities reported during the study follow-up period will be summarized by group. Retrospective death, IS and GE will also be summarised by group.

10.7. Planned interim analysis

No interim analysis is planned.

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

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GSK Biologicals Clinical Report 444563/006 dated November 14, 2003. A phase IIb, double–blind, randomised, 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.

GSK Biologicals Clinical Report 444563/007 dated 17 November 2003. A phase IIb, double–blind, randomised, placebo–controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants previously uninfected with HRV and approximately 3 months of age, when administered concurrently with DTPa–IPV/Hib and HBV vaccines.

GSK Biologicals Clinical Report 444563/023 dated November 2004. A phase III, double–blind, randomised, placebo–controlled, multi–country and multi–center study to assess the efficacy, safety and immunogenicity of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants.

GSK Biologicals Clinical Report 444563/036 dated June 11, 2004. A phase IIIb, double–blind, randomised, placebo–controlled, multi–country and multi–center study to assess the efficacy, safety and immunogenicity of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants in co–administration with specific childhood vaccines.

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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 fulfilment 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.

10. 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.

11. 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.

12. 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)

1. 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.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. 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.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. 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).

6. 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)

1. 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.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. 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 and equipment 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 or Investigator Biography and other credentials (e.g., medical license number in the United States) to GSK and—where required—to relevant authorities. It is recommended that this documentation indicates any previous clinical research experience and history of training in GCP.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To prepare and maintain adequate subject source data or raw data designed to record observations, and other data pertinent to the study.
- To conduct the study in compliance with the protocol any amendment and "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.

II. Protocol Amendments and Administrative changes

- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.

III. Sponsor's Termination of Study

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Remote Data Entry Instructions

Remote Data Entry (RDE) will be used as the method for data collection, which means that subject information will be entered into a computer at the investigational site preferably within 5 working days of becoming available. The site will be capable of modifying the data to assure accuracy with source documentation. All new/updated information will be reviewed and verified by a GSK Biologicals' representative. This information will finally be stored in a central database maintained by GSK Biologicals. At the conclusion of the study, GSK Biologicals will archive the study data in accordance with internal procedures. In addition, the investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site.

Specific instructions for use of RDE will be included in the training material provided to the investigational site.

V. Monitoring by GSK Biologicals

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.

These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document verification (verifying RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the eCRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK 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 agencies and GSK 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, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK 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 GSK Biologicals' sponsored studies are in accordance with GCP 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. GSK's audits entail review of source documents supporting the adequacy and accuracy of eCRFs, review of documentation required to be maintained, and checks on vaccine accountability. GSK's audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring GSK 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
- Study personnel
- Study file
- Safety reporting
- IRB/IEC and regulatory authority approvals
- Facilities
- monitoring
- Vaccine accountability
- Approved study protocol and amendments and investigator brochure
- Informed consent of the subjects (written consent [or witnessed oral if applicable])
- Medical records and other source documents supportive of eCRF data
- Reports to the IRB/ IEC and the sponsor
- Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:
All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:
Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:
For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any

inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

Appendix C Overview of the Recruitment Plan

- The open, long-term follow-up study will be conducted in multiple sites in Finland.
- At the time of initiation of the study, the investigator will contact ALL subjects who completed the primary vaccination study (eTrack No.102247) from the centres in Finland. If at the time of initiation of the long-term study, any parent/guardian of the subject declines participation, refusal will be documented as instructed on the "subject tracking document" provided by GSK Biologicals. The information will be entered in the GSK Biologicals' clinical database for use in identification of any safety issue(s) that may have prevented a subject's participation.
- The intended duration of the study, per subject, will be approximately six months.

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Stool Samples

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

Parents/ guardians will be instructed to collect any stool samples during the GE episodes in the plastic bags/ tubes provided by GSK Biologicals. The samples will be collected each time there is a GE episode.

2. Labelling

The parents/ guardians should complete the label provided on the plastic bag/ tube label with a black ink or ballpoint pen and return the collected stool samples to the study personnel.

If necessary, any hand-written additions to the labels by the study personnel should be made using indelible ink.

3. Sorting and storage

- The plastic tubes and bags with stool specimens should be stored in a home freezer until it is transferred to the investigator's laboratory.
- All the stool samples will be frozen in the laboratory. Wherever possible, a backup facility for storage of stool samples should be available.
- A standard Biological Specimen Listing Form, specifying the samples being shipped for individual subjects at each time point, should be prepared for each shipment. 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 stool samples.
- GSK Biologicals' will organise a dry ice transportation of the stool samples collected to the [redacted] laboratory.

Appendix E Laboratory Assays

The document is supplied as a separate PDF file.

PROTOCOL

Protocols Number EIA20010502	[redacted]	Page number 1 of 4
Version no. 1.0	**Detection of Rotavirus Antigen by ELISA**	Date:
Prepared by:	[redacted] Medical laboratory technologist	21.01.2001
Approved by:	[redacted] Laboratory supervisor	

Method The IDEIA™ Rotavirus test is an immunoassay for the detection of Group A rotaviruses in faecal specimens.

The test utilises a polyclonal antibody to detect group specific proteins, including the major inner capsid protein (VP6), present in Group A rotaviruses. Microwell plates are coated with a rotavirus specific rabbit polyclonal antibody. Sample is added to the microwell simultaneously with a rotavirus specific antibody conjugated to a horseradish peroxidase enzyme. Rotavirus antigen present in the sample is captured between antibody on the solid phase and the enzyme-conjugated antibody. The presence of specifically bound enzyme labelled antibody in the wells results in a colour change, which is stopped by the addition of acid. Colour intensity significantly above background levels is indicative of the presence of the rotavirus antigen in the specimen or control. A plate reader reads results photometrically.

Samples Infant stool specimens, stored at –20 °C.

Controls As a negative control is used the IDEIA™ Rotavirus kit Reagent 1 (sample diluent) and as a positive control is used the IDEIA™ Rotavirus kit Reagent 2 (inactivated bovine rotavirus). At least one positive control and one negative control should be included in 32 samples.

Reagents Double distilled H_2O, ddH_2O

IDEIA™ Rotavirus kit (Dako / Oy Algol Ab, Code No. K6020). Store at +2-8 °C in room 5-135 or in refrigerator room 5-131.

Reagent 1, Sample diluent:
Tris buffered saline, TBS, containing antimicrobial agent and red dye. In case of slight precipitation, re-dissolve by allowing it to reach room temperature.

Reagent 2, Positive control:
Inactivated bovine rotavirus (calf rotavirus strain 3209176, approximately 10^5 infectious forming units / ml prior to inactivation) in buffer containing antimicrobial agent and red dye. Mix gently before use. Handle and dispose as potentially infectious.

PROTOCOL

Protocols Number EIA20010502	[redacted]	Page number 2 of 4
Version no 1.0	**Detection of Rotavirus by ELISA from Human Stool Specimens**	Effective date: 21.01.2001

Reagent 3, Conjugate:
Rotavirus specific rabbit polyclonal antibody conjugated to horseradish peroxidase in a buffered protein solution containing antimicrobial agent and blue dye.

Reagent 4, Washing buffer concentrate (x 25):
Tris buffered solution containing antimicrobial agent and detergent. Dilute washing buffer concentrate as required on the day of use, by adding 1 part concentrate to 24 parts fresh ddH_2O. See the instructions on the bottle.

Reagent 5, Substrate:
Stabilized peroxidase and 3,3'-5,5'-tetramethylbensidine (TMB) in a dilution buffer solution. Avoid direct exposure to TMB use personal protective equipment.

Reagent 6, Stopping solution:
0,46 M Sulphuric Acid.

Supplies IDEIA™ Rotavirus kit (Dako / Oy Algol Ab, Code No. K6020). Store at +4 °C.
Microwell plates coated with a rotavirus specific rabbit polyclonal antibody. (The 96 wells are presented in a microtitration plate frame with 12 plastic holders, each containing break-apart 8 well strips).

Scotch No. 845 Book Tape (Scotch)

Equipment
-Jouan CR 412 centrifuge (Berner, Germany)
-Laser Jet 5L printer (Hewlett Packard, U.S.A)
-Rosenlew Vähävirtanen refrigerator (Rosenlew, Finland)
-Techmatic TM1 Vortex (Labo Team Oy, Germany)
-Victor™ 1420 Multilabel counter with BRAVO MS 5100 computer and AST Vision 5L screen (Wallac Oy, Finland)
-WW004 Wellwash 4 microplate washer with Denley Wellwash 4 program card "4 wash, 8 way head" (Denley Instruments Ltd, UK)
-Zanussi ZAC 280 freezer (Zanussi, Finland)

Procedure The procedure is carried out in room 5-135 or 5-136.
More information instructed in IDEIA™ Rotavirus kit handbook.
Instruction for the use of microplate washer and Victor™ 1420 Multilabel counter see Equipment User Guide / Wellwash 4 microplate washer, WWOO4.

Preparation of faecal specimens
1. Take samples from freezer (no. 24276) and let them thaw in room temperature (RT) about 20 minutes.

[redacted]

PROTOCOL

Protocols Number EIA20010502	[redacted]	Page number 3 of 4
Version no 1.0	**Detection of Rotavirus by ELISA from Human Stool Specimens**	Effective date: 21.01.2001

2. Prepare a 10 % stool suspension. Take about 0,1 g (or 100 µl if liquid) stool specimen by Pasteur pipette to a 1,5 ml eppendorf tube and add 1 ml of sample diluent (Reagent 1). If the stool specimen is very small, take only about 50 mg stool specimen and add 500 µl sample diluent.
   Specimens suspended in sample diluent may be stored at +4 °C for up to 8 days prior to testing.
3. Mix thoroughly about 30 seconds and incubate for 10 minutes RT. Centrifuge 10 minutes at 3000 rpm (1000 x g) in RT (room 5-136).

Sample addition

4. Remove and break off sufficient wells for samples and controls and insert them firmly into the plastic strip holder.
5. Pipet 100 µl of each diluted faecal specimen to the separate microwells. There should be two parallel volumes of each sample. Always pipet the samples carefully into the middle of the wells without touching the walls or bottom of the wells.
6. Pipet 100 µl of the negative control (Reagent 1) and drop 2 drops of the positive control (Reagent 2) to the microwells. At least one positive control and one negative control must be included in each 32 samples.

Conjugate addition

7. After addition of samples and controls to the wells, add 2 drops of conjugate (Reagent 3) to each microwell. Cover the plate with Scotch book tape and mix gently.

First incubation

8. Incubate microwells at RT for 60 ± 5 minutes.

Washing the wells

Wash the contents of the wells by microplate washer (*Denley Wellwash 4* program card *"4 wash, 8 way head"*). Use freshly prepared washing buffer (diluted reagent 4).

1. Remove the tape from the plate, and switch on the washer (button behind).
2. Check the program card in the washer, usually *Denley Wellwash 4* program card *"4 wash, 8 way head"*.
3. Fill the rinse bottle with ddH_2O and load the wash comb to the washer. Prime several times (5 ×) with ddH_2O. Change buffer 4 to the rinse bottle.
4. Load the microwell plate to the washer so that A1 is located to the right upper corner.
5. Push the *prime* button to fill the tubes.
6. Choose number of strips to be washed and put *start* button.
7. After washing, tap the plate empty against cellulose paper.
8. Change ddH_2O to the rinse bottle and prime several times. Leave the cap of the rinse bottle open. Take of the comb and put it in the ddH_2O.

[redacted]

PROTOCOL

Protocols Number EIA20010502	[redacted]	Page number 4 of 4
Version no 1.0	**Detection of Rotavirus by ELISA from Human Stool Specimens**	Effective date: 21.01.2001

Substrate addition
9. Add 2 drops of substrate (Reagent 5) to each microwell.
10. Gently mix the contents of the microwells.

Second incubation
11. Incubate in dark at RT for 10 minutes. (Wells can be read visually immediately after the second incubation.)

Stopping the reaction
12. Stop the substrate reaction by adding 2 drops of stopping solution (Reagent 6) to each well.

Reading (room 5-145)
Read the plate by Victor^2 1420 Multilabel counter at 450 nm within 30 minutes.
See protocol "Use of WW004 Wellwash 4 microplate washer and Victor^2 1420 Multilabel counter" in Protocols folder or in file [redacted] or in Wallac 1420 VICTOR^2 manual.

Results

Interpretation of data

Negative control:
In photometric determination the negative control value should be less than 0.150 absorbance units.

Positive control:
The positive control must have value of greater than 0.500 absorbance units.

Cut-off value:
The cut off value is calculated by adding 0.100 absorbance units to the negative control value.

Specimen results:
Any clinical specimen with an absorbance value greater than the cut-off value is positive. Any specimen with an absorbance value less than the cut-off value is considered negative.
A result within 0.010 absorbance units of the cut-off value should be considered equivocal and sample should be repeated. Also other weak positive results should be confirmed by repeating.

[redacted]

Research number _____ Town _____ Box no _____ Stool ☐ Serum ☐

ELISA date _____ Technician _____ List(s) _____ CSF ☐ Other _____

Rotavirus DAKO IDEIA kit ☐ Other kit _____ ☐ Kit lot no. & exp. date _____

	1	2	3	4	5	6	7	8	9	10	11	12
A												
B												
C												
D												
E												
F												
G												
H												

PROTOCOL

Protocol Number PCR20020204	[redacted]	Page number 1 of 5
Version no. 1.2	**Detection and G-Typing of Rotaviruses by RT-PCR**	Date, Signature
Prepared by:	[redacted] Research assistant	10.09.2001
Responsible:	[redacted] Researchers	
Approved by:	[redacted] Laboratory supervisor	

Purpose

To identify rotavirus from RNA by RT-PCR and to G-type the virus by nested PCR.

Method

Group A rotavirus RNA is first amplified by reverse transcriptase polymerase chain reaction (RT-PCR) and further amplified by nested PCR. The first RT-PCR amplification produces a full-length copy of gene 9 (or gene 8), encoding VP7 glycoprotein. In the second (nested) amplification seven (H pool mix) or six (C pool mix) serotype-specific primers are used for amplifying variable regions on gene 9 (or gene 8). These variable regions correspond to different G-serotypes (G1, G2, G3, G4, G8 or G9). Amplification products of different G-types differ in size and they can be separated and recognised by gel electrophoresis.

Equipments

- AlphaDigiDoc™ (Alpha Innotech Incorporation, USA)
- Centrifuge (Qualitron Inc., Korea)
- Eppendorf Zentrifuge 3200 (Netheler-Hinz GmbH, Germany)
- Thermal Cycler 2720 (Applied Biosystems, USA)
- GeneAmp® PCR system 9700 (PE Applied Biosystems, USA)
- Porkka MC 300 Refrigerator (Huurre Group, Finland)
- Power Pac 300 (Bio Rad, USA)
- Sub-Cell® GT Agarose Gel Electrophoresis System (Bio Rad, USA)
- Zanussi ZV270M Freezer (Zanussi, Sweden)

Reagents

- 5x Green GoTaq® Flexi Buffer (Promega, Cat M8305 or M8306 or M8307)
- AmpliTaq® DNA Polymerase 5 U/µl (Applied Biosystems, Cat N808-0156)
- AMV Reverse Transcriptase 10 U/µl (Promega, Cat M5108)
- Aqua Sterilisata Injekt. H_2O (B.Braun MTnr 11886 FIN or Fresenius Kabi VYV 1916) Store at RT.
- dATP, 100 mM (Bulk dNTP's, Promega, Cat. U120 A, order U1240)
- dCTP, 100 mM (Bulk dNTP's, Promega, Cat. U122 A, order U1240)
- dGTP, 100 mM (Bulk dNTP's, Promega, Cat. U121 A, order U1240)
- dTTP, 100 mM (Bulk dNTP's, Promega, Cat. U123 A, order U1240)
- GeneAmp® 10 × PCR buffer II (Applied Biosystems, Cat. N808-0156)
- GeneAmp® 25 mM $MgCl_2$ (Applied Biosystems, Cat. N808-0156)
- GoTaq® DNA polymerase 5 U /µl (Promega, Cat M8305 or M8306 or M8307)
- $MgCl_2$ Solution (GoTaq), 25 mM (Promega, Cat M8305 or M8306 or M8307)
- RNasin® Ribonuclease Inhibitor 40 U/µl (Promega, Cat. N2115)

All the reagents above are stored at –20 ºC unless told otherwise.

PROTOCOL

Protocol Number PCR20020204	[redacted]	Page number 2 of 5
Version no. 1.2	**Detection and G-Typing of Rotaviruses by RT-PCR**	Effective date:

Nucleotide mixture

dNTP mix (2,5 mM each)
Mix 10 µl of each 100 mM nucleotide dATP, dCTP, dGTP and dTTP and add 360 µl of Aqua Sterilisata.

Primers

All primers are synthesised in Sigma-Genosys Ltd. Each primer is diluted to 25 µM (see separate table "Oligos") and stored at -20 ºC (freezer No. 31048). With primers Rota End, Rota hG1, Rota hG2, Rota hG3, Rota hG4, Rota hG8 and Rota hG9 an H pool primer mixture is prepared by mixing 20 µl of each primer. With primers Rota 9Con1, Rota cG1, Rota cG2, Rota cG3, Rota cG4, and Rota cG9 a C pool primer mixture is prepared by mixing 20 µl of each primer. Primer pools described in Table 1 are ready made and stored in aliquots at -20 ºC (freezer No. 31048).

Table 1. Oligonucleotide primers for Rotavirus Group A VP7 G-Typing.

Name	sequence (5´-3´)	position in the gene	product size
Rota Beg*	GGCTTTAAAAGAGAGAATTTCCGTCTGG	1-28 (+)	
Rota End*	GGTCACATCATACAATTCTAATCTAAG	1062-1036 (-)	1062 bp
H pool*			
Rota End	GGTCACATCATACAATTCTAATCTAAG	1062-1036 (-)	
Rota hG1	CAAGTACTCAAATCAATGATGG	314-335 (+)	749 bp
Rota hG2	CAATGATATTAACACATTTTCTGTG	411-435 (+)	652 bp
Rota hG3	CGTTTGAAGAAGTTGCAACAG	689-709 (+)	374 bp
Rota hG4	CGTTTCTGGTGAGGAGTTG	480-498 (+)	583 bp
Rota hG8	GTCACACCATTTGTAAATTCG	178-198 (+)	885 bp
Rota hG9	CTAGATGTAACTACAACTAC	757-776 (+)	306 bp
C pool**			
Rota 9Con1	TAGCTCCTTTTAATGTATGG	37-56 (+)	
Rota cG1	TCTTGTCAAAGCAAATAATG	176-195 (-)	158 bp
Rota cG2	GTTAGAAATGATTCTCCACT	262-281 (-)	244 bp
Rota cG3	GTCCAGTTGCAGTGTTAGC	485-503 (-)	466 bp
Rota cG4	GGGTCGATGGAAAATTCT	423-440 (-)	403 bp
Rota cG9	TATAAAGTCCATTGCAC	131-147 (-)	110 bp

*) Gouvea V et al, J Clin Microb 1990; 28: 276-282
**) Das et al, J Clin Microb 1994; 32: 1820-1822.

Samples

Rotavirus dsRNA is extracted using Boom's silica - guanidine thiocyanate method or QIAamp® Viral RNA Mini Kit (see separate protocols EXTR20020101 "Extraction of Viral Nucleic Acids by Boom's method" and EXTR20020102 "Extraction of Viral RNA by QIAamp® Viral RNA Mini Kit") from the specimens.

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Protocol Number PCR20020204	[redacted]	Page number 3 of 5
Version no. 1.2	**Detection and G-Typing of Rotaviruses by RT-PCR**	Effective date:

Controls

As positive controls reference rotaviruses grown in MA-104 cells (Table 2) can be used. The dsRNA of reference rotaviruses is extracted using the same method as for unknown specimens. Previously tested RT-PCR positive samples which have been confirmed by sequencing can also be used as positive control. There should be at least one positive control in each RT-PCR assay.

Table 2. Reference rotaviruses.

Rotavirus	Serotype	Source
Wa (DxRRV)	G 1	Dr. [redacted] NIH, USA
DS-1	G 2	Dr. [redacted] NIH, USA
RRV (P)	G 3	Dr. [redacted] NIH, USA
ST-3	G 4	Dr. [redacted] NIH, USA
BrB	G 4	Merck, USA
WI79	G 1	Merck, USA

As negative control Aqua Sterilisata H_2O is used in the PCR reactions. There must be one PCR negative control among every 10 unknown samples.

Procedure

When you carry out this procedure, you must carefully fill in the Appendix.

A. RT-reaction and first amplification

1. Make a mixture of Rota Beg and Rota End primers (25 µM) using 1 µl of both primers per one reaction. Divide mixture into PCR tubes (2 µl/tube) (5-141).
2. Transfer the tubes with primer mixture to the NA working area and add 5 µl of the sample-RNA to the tubes (5-137).
3. Spin the tubes and heat them for 5 min at 97 ºC in thermal cycler (program ROTA/INCU97) (5-144A).
4. Prepare the RT-PCR mix on ice, spin and keep it on ice until use (5-141).

1 × RT-PCR mix	(µl)
Aqua Sterilisata H_2O	1,0
10 × PCR buffer II	1,5
25 mM $MgCl_2$ (AB)	2,0
2,5 mM dNTP mix	2,0
AMV RT-enzyme	1,0
RNasin®	0,5
Total	8,0 µl

5. Transfer the PCR tubes from the thermal cycler to an ice bath (5-145, hood) and add 8 µl of RT-PCR mix into the tubes. Spin and incubate them for 60 min at 42ºC in thermal cycler, hold at 8 ºC (program ROTA/RT) (5-144A).

6. Prepare the 1st PCR mix on ice, mix, spin, and keep it on ice until use (5-141).

1 × 1st PCR mix	(µl)
Aqua Sterilisata H_2O	27,0
10 × PCR buffer II	3,5
25 mM $MgCl_2$ (AB)	2,0
2,5 mM dNTP mix	2,0
AmpliTaq DNA polym.	0,5
Total	35,0 µl

7. Place the RT-PCR tubes on ice and add 35 µl of 1st PCR mixture (5-145).
8. Spin the tubes and run the 1st PCR program:

ROTA/PCR1 (GeneAmp 9700, Thermal Cycler 2720)

94 ºC	3 min	
94 ºC	15 sec	} × 30
50 ºC	1 min	
72 ºC	2 min	
72 ºC	5 min	
8 ºC	hold	(The total time of the program is about 2 h 30 min)

B. Second amplification (Nested PCR)

1. Prepare 2nd PCR mix on ice, divide it into PCR tubes (48 µl/tube), and keep the tubes on ice until use (5-141).

1 × 2nd PCR mix	Hpool (µl)	Cpool (µl)
Aqua Sterilisata H_2O	23,5	24,5
5x Green GoTaq Flexi Buffer	10,0	10,0
25 mM $MgCl_2$ (Promega)	3,0	3,0
2,5 mM dNTP mix	4,0	4,0
H pool/C pool primer mix	7,0	6,0
GoTaq DNA polymerase	0,5	0,5
Total	48,0 µl	48,0 µl

2. Add 2 µl of the 1st PCR product to the tubes with 2nd PCR mix. This should be done in the hood on ice (room 5-144A).

3. Spin the tubes and run the 2nd PCR program:
ROTA/PCR2 (GeneAmp 9700, Thermal Cycler 2720)

94 ºC	3 min	
94 ºC	15 sec	} × 25
50 ºC	40 sec	
72 ºC	1 min 10 sec	
72 ºC	5 min	
8 ºC	hold	(The total time of the program is about 1 h 40 min)

PROTOCOL

Protocol Number PCR20020204	[redacted]	Page number 5 of 5
Version no. 1.2	**Detection and G-Typing of Rotaviruses by RT-PCR**	Effective date:

C. Electrophoresis (room 5-144B)

Prepare 1,5 % agarose gel according to separate protocol ELFO20020401 "Electrophoresis". Use the big gel tray with 3 middle-size combs to get 60 wells in the gel. Add loading buffer only to the 1st PCR product; and pipette H and C pool directly into the gel because the 5x Green GoTaq buffer already contains the loading dye. To fit all 20 samples and one marker in each row, pipette the two H_2O negative controls into the same well. To fit 21 samples pipette also the two PBS negative controls together into the same well. Load C pool products into the first lane of the gel, H pool products into the middle lane and 1st PCR products into the lowest lane. Load one molecular marker (3 µl, MBI Fermentas) into the middle of each lane: GeneRuler100 bp DNA Ladder. Run the samples for 90 min at 100 V.

Results

The expected positive PCR product bands in the agarose gel are the following:
In the 1st PCR the full length gene amplicon is 1062 bp
In the 2nd PCR the amplicons specific for different genotypes are:

	H pool	C pool
G 1	749 bp	158 bp
G 2	652 bp	244 bp
G 3	374 bp	466 bp
G 4	583 bp	403 bp
G 8	885 bp	
G 9	306 bp	110 bp

Storing of the samples and filing of the results

Appendix is filed in current study folder "Rotavirus RT-PCR results" in room 5-148. Positive samples are labelled and stored at –20 °C (freezer No. 31047, room 5-146) for sequencing. The following information must be found on the tube labels:

Study, Rota PCR, List, PCR date/Initials
Sample number, Initials, Sample date, Tube, (eg.1C/H/1st)

Tubes are stored in Nalgene-boxes. The following information must be found on the boxes:

Study, Rota PCR, List, PCR date/Initials
Place of the samples in the box

PCR20020204 Version no. 1.2	**Detection and G-Typing of Rotaviruses by RT-PCR**	**Appendix** Page 1 of 2

Worksheet for Rotavirus RT-PCR method

PCR date_____ Initials_____ PCR machine_____

Research_____

Extraction method, List, Date_____

Reagents
5x Green GoTaq® Flexi Buffer (Promega)
Aqua Sterilisata H_2O (Fresenius Kabi)
AmpliTaq® DNA polymerase, 5 U/µl (Applied Biosystems)
AMV Reverse Transcriptase, 10 U/µl (Promega)
dNTP-mix (2,5 mM dATP, dCTP, dTTP and dGTP, Promega)
GeneAmp® 25 mM $MgCl_2$ Solution (Applied Biosystems)
GeneAmp® 10 × PCR buffer II (Applied Biosystems)
GoTaq® DNA polymerase 5 U/µl (Promega)
$MgCl_2$ Solution, 25 mM (Promega)
RNasin® Ribonuclease inhibitor, 40 U/µl (Promega)

Primers (25 µM)

RT and 1st PCR	H pool	C pool
Rota Beg	Rota End	Rota 9Con1
Rota End	Rota hG1	Rota cG1
	Rota hG2	Rota cG2
	Rota hG3	Rota cG3
	Rota hG4	Rota cG4
	Rota hG8	Rota cG9
	Rota hG9	

Sample	1	2	3	4	5	6	7	8	9 H_2O-1	10
RT-PCR										
H pool										
C pool										
Sample	11	12	13	14	15	16	17	18	19 H_2O-2	20
RT-PCR										
H pool										
C pool										
Sample	21 PCR +	22	23	24	25	26	27	28	29	30
RT-PCR										
H pool										
C pool										

Photograph

Results (date, initials)_____ and_____
In computer file_____ and_____
PCR product saved_____
In sequencing file_____

PCR20020204 Version no. 1.2	**Detection and G-Typing of Rotaviruses by RT-PCR**	**Appendix** Page 2 of 2

Date/Initials_____ Research, List etc._____

	× Primer mixture (µl)	
25 µM Beg 9	1,0 ×	=
25 µM End 9	1,0 ×	=

Pipette 2 µl of mixture to empty PCR-tubes, add 5,0 µl of dsRNA, spin ⇒ 5 min at 97°C (ROTA/INCU97), then 5 min on ice.

	× RT-PCR mix (µl)	
Aqua Sterilisata H_2O	1,0 ×	=
10 × PCR buffer II	1,5 ×	=
25 mM $MgCl_2$ (AB)	2,0 ×	=
2,5 mM dNTP	2,0 ×	=
AMV RT-enzyme	1,0 ×	=
RNasin®	0,5 ×	=

Add 8,0 µl of RT-PCR mix to primer-RNA mixture and spin ⇒ 42°C for 1h (ROTA/RT), then 5 min on ice.

	× 1st PCR mix (µl)	
Aqua Sterilisata H_2O	27 ×	=
10 × PCR buffer II	3,5 ×	=
25 mM $MgCl_2$ (AB)	2,0 ×	=
2,5 mM dNTP	2,0 ×	=
AmpliTaq DNA polym	0,5 ×	=

Add 35µl to RT-reaction spin and run the 1st PCR program

1st PCR amplification program: ROTA/PCR1

94 ºC	3 min	
94 ºC	15 s	× 30
50 ºC	1 min	
72 ºC	2 min	
72 ºC	5 min	
8 ºC	hold	

2nd PCR mix		**× H pool (µl)**		**× C pool (µl)**
Aqua Sterilisata H_2O	23,5 ×	=	24,5 ×	=
5x Green GoTaq Flexi Buffer	10,0 ×	=	10,0 ×	=
25 mM $MgCl_2$ (Promega)	3,0 ×	=	3,0 ×	=
2.5 mM dNTP	4,0 ×	=	4,0 ×	=
Hpool/Cpool primer mix (25 µM)	7,0 ×	=	6,0 ×	=
GoTaq DNA polymerase	0,5 ×	=	0,5 ×	=

Pipette 48 µl to PCR-tubes, add 2 µl of 1st PCR-reaction product, spin and run the 2nd PCR program.

2nd PCR amplification program: ROTA/PCR2

94 ºC	3 min	
94 ºC	15 s	× 25
50 ºC	40 s	
72 ºC	1 min 10 s	
72 ºC	5 min	
8 ºC	hold	

Electrophoresis
Prepare 1,5 % agarose gel with 1 x TAE buffer containing 0,08 µg/ml of ethidium bromide. Take 10 µl of each PCR-product. Combine the 1st PCR product with 2 µl of loading buffer. Pipette the H pool and C pool directly into the gel. Add one marker in the middle of each lane. Run the gel ~ 90 min at 100 V.

Visualize under UV illumination and take a photo (see guidelines of AlphaDigiDoc image analyser).

Interpretation of results
The expected positive PCR-product bands are:

1st PCR full length gene: 1062 bp

2nd PCR genotyping	H pool	C pool
G 1	749 bp	158 bp
G 2	652 bp	244 bp
G 3	374 bp	466 bp
G 4	583 bp	403 bp
G 8	885 bp	
G 9	306 bp	110 bp

[redacted]

Appendix F Mathematical Details about Sample Size Determination Sheet

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1 / N1}{n2 / N2} = 1 - \frac{n1}{rn2}$$

where n1 = number of cases in the vaccine group

N1 = number of subjects in the vaccine group

n2 = number of cases in the placebo group

N2 = number of subjects in the placebo group

N1/N2 = r

*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 binomial 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 G Standard Autopsy Questionnaire

Reference: World Health Organization. A standard autopsy method for investigating causes of death in infants and children. Geneva: World Health Organization, 1999:1-78. (WHO/CDS/CSR/ISR/99.4).

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

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GlaxoSmithKline

Sponsor:
GlaxoSmithKline Biologicals
PO Box 24 (Piispansilta 9A),
02231 Espoo, Finland

Study vaccine	GlaxoSmithKline (GSK) Biologicals' live attenuated oral human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	ROTA-036 EXT Y3 (109810)
EudraCT number	2006-006552-36
Date of approval	Final: 29 November 2006
Title	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Clinical & Medical Affairs, Rotarix & N/S Europe, Clinical Development Europe Management. • [redacted] Senior Clinical Trials Manager. • [redacted] Clinical Trials Manager. • [redacted] and [redacted] Biometricians. • [redacted] Manager-Biometrician • [redacted] Director, Worldwide Clin Ops-Biometrics • [redacted] Medical Advisor. • [redacted] Lead Manager, Worldwide Clinical Development, Rotavirus Vaccines.
Sponsor signatory approval	[redacted] Medical Director, MEDICAL, Medical Management.
Sponsor signatory:	
Signature:	[redacted]
Date:	29 Nov 2006

Copyright 2006 the GlaxoSmithKline group of companies. All rights reserved. Unauthorized copying or use of this information is prohibited. CARS Id : **CLIN_200611_2679/** Version : **1.4,Admin. QC/** Modify Date : **30/11/2006**

Investigator Agreement

eTrack study number and abbreviated title	109810 (ROTA-036 EXT Y3)
EudraCT number	2006-006552-36
Title	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).
- That I am aware of, and will comply with, "Good Clinical Practice" (GCP) and all applicable regulatory requirements.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
    - Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
    - Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Prof. [redacted]

[redacted]

Investigator signature

23 Nov 2006

Date

GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
Rota-036 EXT Y3	109810

Date: 08 Dec 2009

Concerns: Protocol Investigator Agreement document / CARS footer

Details:

I confirm that the Investigator Agreement page signed on 29 Nov 2006 by Prof. [redacted] s the valid signature for the study 109810 (Rota-036 EXT Y3) study protocol (final: 29 November 2006).

By mistake signature has been obtained on Investigator Agreement document without the appropriate GSK CARS reference in the footer:
CARS Id: CLIN_200611_2679/Version: 1.4,Admin. QC/ Modify Date: 30/11/2006

Made by: [redacted]

Signature: [redacted]

Function: Clinical operations project Mgr

Signature Date: 08 Dec 09

(If required) Approved by: _____

Approver's Signature: _____

Function: _____

Signature Date: _____

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 18 JAN 2007

Investigator signature **Date**

COPY

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

14 Dec 2007

Investigator signature **Date**

COPY

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature 16 Jun 2009 **Date**

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22 JAN 2007

Investigator signature **Date**

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22JAN2007

Investigator signature **Date**

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 06 FEB 2007

[redacted]**r signature** **Date**

COPY

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

23 JAN 2007

Date

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

28 JAN 2007

Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]tigator signature [redacted] 23.1.07
Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

22 JAN 2007

Date

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

20 Jun 2007

Investigator signature **Date**

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

25 Jan 2002

Date

COPY

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 20 Jun 2007

Investigator signature **Date**

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

23 JAN 2007

Date

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

23 Jan 2007

Date

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

23 Jan 2007

Date

COPY

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 18 JAN 2007

Investigator signature **Date**

COPY

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investigator signature

23 Jan 2007

Date

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted] 22JAN2007

Investigator signature **Date**

Sample Case Report Form

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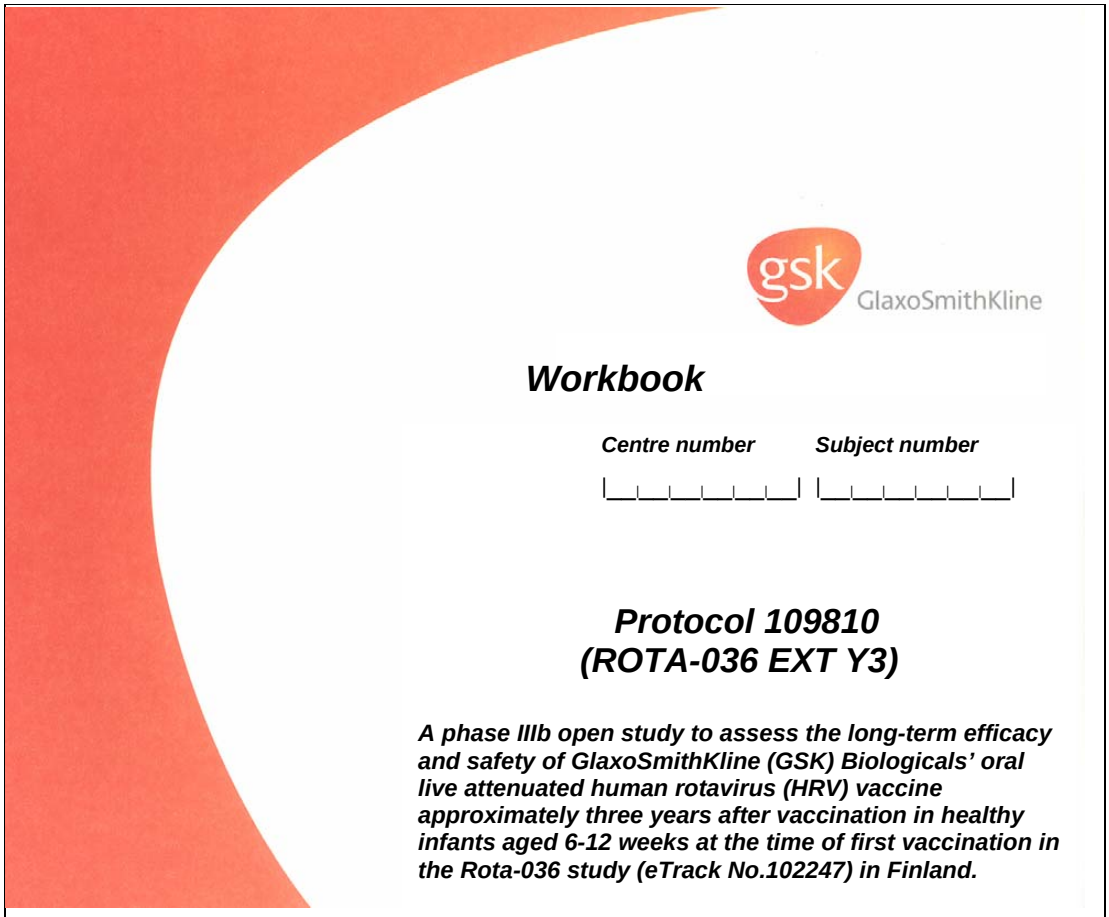

Workbook

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Protocol 109810
(ROTA-036 EXT Y3)

A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

GlaxoSmithKline Biologicals

PO Box 24 (Piispansilta 9A), 02231 Espoo, Finland
Tel: [redacted]

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GENERAL INSTRUCTIONS

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.

DATES

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 7| = 1st January 2007
day month year

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Study Conclusion** form**.**

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ADVERSE EVENT DEFINITIONS

GASTROENTERITIS EPISODE :
Diarrhea with or without vomiting. Two occurrences of diarrhoea should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.

DIARRHEA :
Passage of three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: 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).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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 / Resolved
2: Recovering / Resolving: Subject is recovering at the time she/he completes the study or at the time she/he withdraws from study.
3: Not recovered / Not resolved: AE is ongoing at the time the subject completes the study or becomes lost to follow-up; in case of death AEs that are not the cause of death.
4: Recovered with sequelae / Resolved with sequelae
5: Fatal: AE is the cause of death (only applicable for SAE reports)

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
- prolongation of existing hospitalization
- is a congenital anomaly / birth defect in the offspring of a study subject
- In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

SAEs will not be routinely collected by GSK during the follow-up period. However, GSK has to be informed if the investigator becomes aware of any unusual safety information or any safety information that appears to be drug related in a similar spirit as if an individual had completed the study.

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109810 (ROTA-036 EXT Y3)

FLOW SHEET

List of study procedures

	Timing: Beginning of January 2007 up to the end of June 2007
Informed consent	●
Check inclusion criteria at long-term follow-up time point	●
Check elimination criteria	●
Medical history	●
Reporting of all GE since the last visit in the 2nd yr follow up	●
Retrospective collection of cases of IS and mortality since the last visit in the 2nd yr follow-up	●
Collection of stool samples if the child develops GE	●
Reporting of all GE during the follow-up period	●
Reporting of SAEs during the follow-up period	●
Reporting of mortality during the follow-up	●
Reporting of AEs leading to subject withdrawal and drop out	●
Telephone contact or SMS	●
Return of GE diary cards	●
Diary card transcription by investigator	●
Study Conclusion	●

● is used to indicate a study procedure which requires documentation in the eCRF.

It is the investigator's responsibility to ensure that the interval between the previous follow-up (at year two) and the current follow-up visit are followed as closely as possible.

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Timing: Beginning of January 2007 up to the end of June 2007

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REMINDERS

INFORMED CONSENT

Informed Consent has to be obtained prior to any study procedure

ELIMINATION CRITERIA

Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

Please report adverse events as specified in the Protocol and fill in the **Non-Serious Adverse Events** section or a **Serious Adverse Event (SAE)** report, as appropriate. SAE must be submitted to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

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Protocol

109810 (ROTA-036 EXT Y3)

ELIMINATION CRITERIA DURING THE STUDY

If any of the elimination criteria become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the long-term follow-up.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the long-term follow-up. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)

[C] Administration of immunoglobulins and/or any blood products during the long-term follow-up period.

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109810 (ROTA-036 EXT Y3)

Protocol		Visit	Date of follow-up	Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__| Day month year

DEMOGRAPHICS

Previous study number : 102247/036 (Rota-036) Same subject number as in previous study

Center number: |__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender:
[M] ☐ Male
[F] ☐ Female

Ethnicity:
[1] ☐ American Hispanic or Latino
[2] ☐ Not American Hispanic or Latino

Race:
[1] ☐ African Heritage / African American
[2] ☐ American Indian or Alaskan Native
[3] ☐ Asian - Central/South Asian Heritage
[4] ☐ Asian - East Asian Heritage
[5] ☐ Asian - Japanese Heritage
[6] ☐ Asian - South East Asian Heritage
[7] ☐ Native Hawaiian or Other Pacific Islander
[8] ☐ White - Arabic / North African Heritage
[9] ☐ White - Caucasian / European Heritage
[99] ☐ Other, specify _____

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		_____

ELIGIBILITY CHECK

Did the subject meet all the entry criteria?

☐ Yes ☐ No → If No, tick (✓) all boxes corresponding to violations of any inclusion criteria.

Do not enter the subject into the study if he/she failed any inclusion criteria below.

INCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the inclusion criteria the subject failed.

[1] ☐ A male or female who has completed the second year efficacy follow-up of the primary vaccination study (Rota-036, eTrack No.102247) in Finland.

[2] ☐ Written informed consent obtained from the parent or guardian of the subject.

EXCLUSION CRITERIA

Not applicable as this study is a long-term efficacy and safety follow-up of subjects who have received the HRV vaccine or the placebo dose in the primary vaccination study (Rota-036).

2.

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		_____

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions, signs or symptoms present since end of the 2nd follow-up period up to the start of the follow-up for the 3rd year?

☐ No ☐ Yes → Please give diagnosis and tick (✓) appropriate Past/Current box(es).

MedDRA System Organ Class	DIAGNOSIS	PAST	CURRENT
[1] **Skin and subcutaneous tissue**	.....	☐	☐
	.....	☐	☐
[2] **Musculoskeletal and connective tissue**	.....	☐	☐
	.....	☐	☐
[3] **Cardiac**	.....	☐	☐
	.....	☐	☐
[4] **Vascular**	.....	☐	☐
[5] **Respiratory, thoracic and mediastinal**	.....	☐	☐
	.....	☐	☐
[6] **Gastrointestinal**	.....	☐	☐
	.....	☐	☐
[7] **Hepatobiliary**	.....	☐	☐
[8] **Renal and urinary**	.....	☐	☐
[9] **Nervous system**	.....	☐	☐
[10] **Eye**	.....	☐	☐
[11] **Ear and labyrinth**	.....	☐	☐
[12] **Endocrine**	.....	☐	☐
[13] **Metabolism and nutrition**	.....	☐	☐
[14] **Blood and lymphatic system**	.....	☐	☐
[15] **Immune system** (incl allergies, autoimmune disorders)	.....	☐	☐
	.....	☐	☐
[16] **Infections and infestations**	.....	☐	☐
[17] **Neoplasms benign, malignant and unspecified** (incl cysts, polyps)	.....	☐	☐
[18] **Surgical and medical procedures**	.....	☐	☐
	.....	☐	☐
[99] **Other**	.....	☐	☐
	.....	☐	☐

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

3.

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GASTROENTERITIS

Reported between the end of the 2nd Yr efficacy FU up to the start of the 3rd Yr FU

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		|__|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present diarrhea since the end of the 2nd year follow-up?

☐ No
☐ Yes, If yes → Please report in the **Gastroenteritis** section.

INTUSSUSCEPTION

Did the subject experience any intussusceptions since the end of the 2nd year follow-up?

☐ No
☐ Yes, If yes → please specify how many intussusceptions: |__\|__|

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GASTROENTERITIS EPISODES

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported between the end of the 2nd Year efficacy FU up to the start of the 3rd Year FU)*

Has any gastroenteritis occurred since the end of the second year follow-up?

☐ No
☐ Yes → Please complete below.

Episode n° |__|__|

Treatment: ☐ Unknown
☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Medical advice: ☐ Unknown
☐ No
☐ Yes → |__|__| HO/MD/ER/AD

Medically attended visit: (Refer to protocol for full definition)
HO: Hospitalisation
ER: Emergency room
MD: Medical personnel
AD: Medical contact without visit

Vomiting:

☐ No
☐ Yes →please specify the duration of vomiting from onset of GE: |__|__| days

→please specify the highest number of vomits per day from onset of GE: |__|__|

☐ Unknown

Looser than normal stools:

☐ No
☐ Yes →please specify the duration of looser than normal stools from onset of GE: |__|__| days

→please specify the highest number of looser than normal stools per day from onset of GE: |__|__|

☐ Unknown

Fever:

Was there any temperature above 36.6°C (Axillary) or 37.1°C (rectal)?

☐ No
☐ Yes →please specify the duration of temperature above specified value from onset of GE: |__|__| days

→please specify the highest temperature from onset of GE: |__|__| . |__| °C

☐ Not taken

Behavioural symptoms:

Was there any behavioural symptoms

☐ No
☐ Yes →please specify:

☐ Irritability ☐ Lethargy ☐ Listless ☐ Seizure ☐ Others: _____

☐ Unknown

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported between the end of the 2nd Year efficacy FU up to the start of the 3rd Year FU)*

Episode n° |__|__|

Treatment: ☐ Unknown
☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Medical advice : ☐ Unknown
☐ No
☐ Yes → |__|__| HO/MD/ER/AD

Medically attended visit: HO: Hospitalisation
(Refer to protocol for full definition) ER: Emergency room
MD: Medical personnel
AD: Medical contact without visit

Vomiting:

☐ No
☐ Yes →please specify the duration of vomiting from onset of GE: |__|__| days
→please specify the highest number of vomits per day from onset of GE: |__|__|
☐ Unknown

Looser than normal stools:

☐ No
☐ Yes →please specify the duration of looser than normal stools from onset of GE: |__|__| days
→please specify the highest number of looser than normal stools per day from onset of GE: |__|__|
☐ Unknown

Fever:

Was there any temperature above 36.6°C (Axillary) or 37.1°C (rectal)?

☐ No
☐ Yes →please specify the duration of temperature above specified value from onset of GE: |__|__| days
→please specify the highest temperature from onset of GE: |__|__| . |__| °C
☐ Not taken

Behavioural symptoms:

Was there any behavioural symptoms

☐ No
☐ Yes →please specify:
☐ Irritability ☐ Lethargy ☐ Listless ☐ Seizure ☐ Others: _____
☐ Unknown

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported between the end of the 2nd Year efficacy FU up to the start of the 3rd Year FU)*

Episode n° |__|__|

Treatment: ☐ Unknown
☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Medical advice : ☐ Unknown
☐ No
☐ Yes → |__|__| HO/MD/ER/AD

Medically attended visit: HO: Hospitalisation
(Refer to protocol for full definition) ER: Emergency room
MD: Medical personnel
AD: Medical contact without visit

Vomiting:

☐ No
☐ Yes →please specify the duration of vomiting from onset of GE: |__|__| days

→please specify the highest number of vomits per day from onset of GE: |__|__|

☐ Unknown

Looser than normal stools:

☐ No
☐ Yes →please specify the duration of looser than normal stools from onset of GE: |__|__| days

→please specify the highest number of looser than normal stools per day from onset of GE: |__|__|

☐ Unknown

Fever:

Was there any temperature above 36.6°C (Axillary) or 37.1°C (rectal)?

☐ No
☐ Yes →please specify the duration of temperature above specified value from onset of GE: |__|__| days

→please specify the highest temperature from onset of GE: |__|__| . |__| °C

☐ Not taken

Behavioural symptoms:

Was there any behavioural symptoms

☐ No
☐ Yes →please specify:

☐ Irritability ☐ Lethargy ☐ Listless ☐ Seizure ☐ Others: _____

☐ Unknown

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		Beginning of January 2007 up to the end of June 2007		|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported between the end of the 2nd Year efficacy FU up to the start of the 3rd Year FU)*

Episode n° |__|__|

Treatment: ☐ Unknown
☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Medical advice : ☐ Unknown
☐ No
☐ Yes → |__|__| HO/MD/ER/AD

Medically attended visit: HO: Hospitalisation
(Refer to protocol for full definition) ER: Emergency room
MD: Medical personnel
AD: Medical contact without visit

Vomiting:

☐ No
☐ Yes →please specify the duration of vomiting from onset of GE: |__|__| days

→please specify the highest number of vomits per day from onset of GE: |__|__|

☐ Unknown

Looser than normal stools:

☐ No
☐ Yes →please specify the duration of looser than normal stools from onset of GE: |__|__| days

→please specify the highest number of looser than normal stools per day from onset of GE: |__|__|

☐ Unknown

Fever:

Was there any temperature above 36.6°C (Axillary) or 37.1°C (rectal)?

☐ No
☐ Yes →please specify the duration of temperature above specified value from onset of GE: |__|__| days

→please specify the highest temperature from onset of GE: |__|__| . |__| °C

☐ Not taken

Behavioural symptoms:

Was there any behavioural symptoms

☐ No
☐ Yes →please specify:

☐ Irritability ☐ Lethargy ☐ Listless ☐ Seizure ☐ Others: _____

☐ Unknown

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GASTROENTERITIS

Reported during the study period for the long term follow-up

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109810 (ROTA-036 EXT Y3)

Protocol		Visit		Subject Number
109810		**Beginning of January 2007 up to the end of June 2007**		|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Has the subject presented diarrhea during the study period for the long-term follow-up? (Beginning of Jan2007 up to the end of June 2007)

☐ No
☐ Yes, If yes → Please report in the **Gastroenteritis** section.

SERIOUS ADVERSE EVENT / INTUSSUSCEPTION

Has the subject experienced any Serious Adverse Event during the study period for the long-term follow-up?

☐ No
☐ Yes, If yes → please specify how many serious adverse events: |__|__|

→ please complete the SAE report form for each SAE if not done before.

Among the SAE's, is there any intussusception during the study period for the long-term follow- up?

☐ No
☐ Yes, If yes → please specify how many intussusceptions: |__|__|

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GASTROENTERITIS EPISODES

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GlaxoSmithKline

109810 (ROTA-036 EXT Y3)

Protocol					Subject Number
109810				**Beginning of January 2007 up to the end of June 2007**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported during the study period for the long term follow-up)*

Has any gastroenteritis occurred during the study period for the long-term follow-up? ☐ No ☐ Yes → Please complete below and next pages if necessary.

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

One single stool sample should be collected as soon as possible following the start of the gastroenteritis episode.

A second stool sample can be taken if the first one is insufficient.

Medical advice : ☐ No
☐ Yes → |__|__| HO/MD/ER/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Medically attended visit : HO : Hospitalisation
ER : Emergency room
MD : Medical personnel
AD: Medical contact without visit
(Refer to protocol for full definition)

Route: ☐ Axillary
☐ Rectal

The first and last date to be considered is the first and last date with at least 3 looser than normal stools.

Date day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	Not Taken	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

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109810 (ROTA-036 EXT Y3)

Protocol					Subject Number
109810				**Beginning of January 2007 up to the end of June 2007**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE(*Reported during the study period for the long term follow-up)*

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical advice : ☐ No
☐ Yes → |__|__| HO/MD/ER/AD

One single stool sample should be collected as soon as possible following the start of the gastroenteritis episode.

A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Medically attended visit : HO : Hospitalisation
ER : Emergency room
MD : Medical personnel
AD: Medical contact without visit
(Refer to protocol for full definition)

Route: ☐ Axillary
☐ Rectal

The first and last date to be considered is the first and last date with at least 3 looser than normal stools.

Date day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	Not Taken	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

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109810 (ROTA-036 EXT Y3)

Protocol					Subject Number
109810				**Beginning of January 2007 up to the end of June 2007**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported during the study period for the long term follow-up)*

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

Medical advice : ☐ No
☐ Yes → |__|__| HO/MD/ER/AD

One single stool sample should be collected as soon as possible following the start of the gastroenteritis episode.

A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Medically attended visit : HO : Hospitalisation
ER : Emergency room
MD : Medical personnel
AD: Medical contact without visit
(Refer to protocol for full definition)

Route: ☐ Axillary
☐ Rectal

The first and last date to be considered is the first and last date with at least 3 looser than normal stools.

Date day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	Not Taken	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

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109810 (ROTA-036 EXT Y3)

Protocol					Subject Number
109810				**Beginning of January 2007 up to the end of June 2007**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE (*Reported during the study period for the long term follow-up)*

Episode n° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: ____________________

One single stool sample should be collected as soon as possible following the start of the gastroenteritis episode.

A second stool sample can be taken if the first one is insufficient.

Medical advice : ☐ No
☐ Yes → |__|__| HO/MD/ER/AD

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Medically attended visit : HO : Hospitalisation
ER : Emergency room
MD : Medical personnel
AD: Medical contact without visit
(Refer to protocol for full definition)

Route: ☐ Axillary
☐ Rectal

|__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools.

Date day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	Not Taken	Irritability / Less playfull	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

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Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
IN	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject or subject's parents/guardians about any medication(s) taken.

- SEE PROTOCOL

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109810 (ROTA-036 EXT Y3)

Protocol				Subject Number
109810				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments been administered during the time frame as specified in the Protocol?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick 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					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

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NON-SERIOUS ADVERSE EVENTS

During the study period for the long-term follow-up

To be filled only in case of withdrawal due to non-serious AE.

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Protocol				Subject Number
109810				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL

(Please report **serious adverse events** only on the **Serious Adverse Event (SAE)** reports).

Has any **non-serious adverse events** occurred within long-term follow-up?

☐ No
☐ Yes, please complete the following table.

AE No.	1	2
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medically attended visit (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalisation ER: Emergency Room MD: Medical Personnel	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

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109810 (ROTA-036 EXT Y3)

Protocol					Subject Number
109810					|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO WITHDRAWAL (continued)

AE No.	3	4
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe	[1] ☐ Mild [2] ☐ Moderate [3] ☐ Severe
Relationship to investigational products: Is there a reasonable possibility that the AE may have been caused by the investigational product?	[N] ☐ No [Y] ☐ Yes	[N] ☐ No [Y] ☐ Yes
Outcome	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae	[1] ☐ Recovered / Resolved [2] ☐ Recovering / resolving [3] ☐ Not recovered / not resolved [4] ☐ Recovered with sequelae / Resolved with sequelae
Medically attended visit (Refer to protocol for full definition.) If yes please specify type: HO: Hospitalisation ER: Emergency Room MD: Medical Personnel	[N] ☐ No [Y] ☐ Yes → type: |__|__|	[N] ☐ No [Y] ☐ Yes → type: |__|__|

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STUDY

CONCLUSION

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109810 (ROTA-036 EXT Y3)

Protocol				Subject Number
109810				_____

STUDY CONCLUSION OF THE LONG-TERM FOLLOW-UP

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study period for the long-term follow-up?

☐ No ☐ Yes → Specify: _____

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109810 (ROTA-036 EXT Y3)

Protocol				Subject Number
109810				|__|__|__|__|__|__|

STUDY CONCLUSION OF THE LONG-TERM FOLLOW-UP (continued)

Was the subject withdrawn from the study?

☐ No

☐ Yes → Major reason for withdrawal (tick **one** box only).

☐ [SAE] Serious adverse event
→ Please complete and submit SAE report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete Non-serious Adverse Event section
→ Please specify AE No. |__|__|

☐ [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: _____

→ Who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

→ Date of last contact: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Was the subject in good condition at date of last contact?
☐ No → Please give details in Adverse Events section
☐ Yes

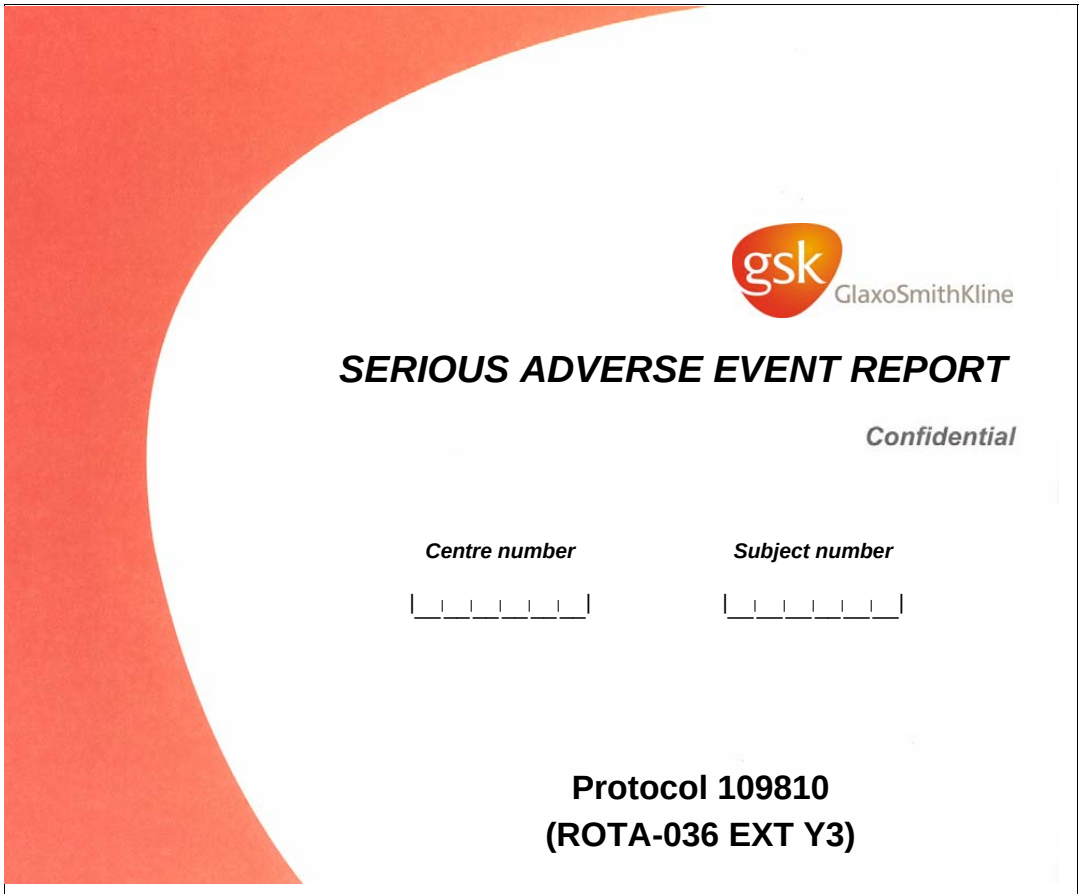
INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

CONFIDENTIAL



SERIOUS ADVERSE EVENT REPORT

Confidential

Centre number |__|__|__|__|__|__|

Subject number |__|__|__|__|__|__|

Protocol 109810
(ROTA-036 EXT Y3)

GlaxoSmithKline Biologicals
Rue de l'Institut 89,
B – 1330 Rixensart, Belgium
Tel: [redacted]

SAE Report - Version 12.3 – JANUARY 31, 2007

GlaxoSmithKline

Protocol (eTrack number) 109810 Abbreviated Title ROTA-036 EXT Y 3	Country	Center Number	Subject Number	Treatment Number
	_____	|__|__|__|__|__|__|	|__|__|__|__|__|__|	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

SAE Report N° |__|__| GSK receipt date: |__|__||__|__|__||__|__|

☐ 1. Initial report ☐ 2. First follow-up ☐ 3. Second follow-up ☐ 4. Third follow-up

SECTION 1

Event	Start date	Outcome	End date	Maximum intensity	Action taken with investigational product(s) as a result of the SAE	Withdrawal	Relationship to investigational product(s)	Medically attended visit
Diagnosis only (if known), otherwise sign / symptom	Day Month Year (DD MMM YY)	1: Recovered / resolved 2: Recovering / resolving 3: Not recovered / not resolved 4: Recovered / resolved with sequelae 5: Fatal	If fatal, record date of death Day Month Year (DD MMM YY)	1: Mild 2: Moderate 3: Severe X: Not applicable	1: Investigational product(s) withdrawn 2: Dose not changed 3: Dose Interrupted X: Not applicable	Did the subject withdraw from study as a result of this SAE? Y = Yes* N = No	Is there a reasonable possibility that the SAE may have been caused by the investigational product? Y = Yes N = No	**HO**: Hospitalisation **ER**: Emergency Room **MD**:Medical Doctor *(Refer to protocol for full definition)*
	|__|__|__|__|__|__|		|__|__|__|__|__|__|					
	|__|__|__|__|__|__|		|__|__|__|__|__|__|					
	|__|__|__|__|__|__|		|__|__|__|__|__|__|					

** Withdrawal : If Yes, please complete the **Study Conclusion** page in the CRF of the subject and tick **SAE** as reason for withdrawal*

If fatal, was a post-mortem/autopsy performed? ☐ No ☐ Yes → *Summarize findings in Section 11 Narrative Remarks of this SAE form.*

SECTION 2 - Seriousness *specify reason(s) for considering this a SAE, tick all that apply:*

☐ Results in death

☐ Is life threatening

☐ Requires hospitalisation or prolongation of existing hospitalisation

→ date of admission |__|__||__|__|__||__|__|__|__|

→ date of discharge |__|__||__|__|__||__|__|__|__|

☐ Results in disability / incapacity

☐ Congenital anomaly / birth defect in the offspring

☐ Other (clinically significant / intervention required) (see definition of SAE)

→ specify _____

Protocol (eTrack number) 109810 Abbreviated Title ROTA-036 EXT Y 3	Country	Center Number	Subject Number	Treatment Number
	_____	|__|__|__|__|__|__|	|__|__|__|__|__|__|	|__|__|__|__|__|

SECTION 3 - Demography Data

Date of birth: (Day Month Year) |__|__| |__|__|__| |__|__|__|__|

Sex: ☐ Male ☐ Female

Weight: |__|__|__|.|__| kg

US only Pounds: |__|__|__| Ounces: |__|__|

SECTION 4 *If investigational product was stopped, did the reported event(s) recur after further investigational product(s) were administered?*

☐ No ☐ Yes ☐ Unknown at this time ☐ Not applicable

SECTION 5 – Possible causes of SAE other than investigational product: *(tick all that apply)*

☐ Disease under study *(not applicable for prophylactic vaccine studies)*
☐ Medical condition(s) (*record in Section 6*)
☐ Lack of efficacy
☐ Withdrawal of investigational product
☐ Concomitant medication (*record in Section 8)*
☐ Activity related to study participation (e.g. procedures)
☐ Other, specify: _____
_____

SECTION 6 – Relevant Medical Conditions

Specify any RELEVANT past or current medical disorders, allergies, surgeries, etc., that can help explain the SAE	Date of onset Day Month Year (DD MMM YY)	Condition present at time of SAE	If No, date of last occurrence Day Month Year (DD MMM YY)
	|__|__||__|__|__||__|__|__|__|	☐ Yes ☐ No →	|__|__||__|__|__||__|__|__|__|
	|__|__||__|__|__||__|__|__|__|	☐ Yes ☐ No →	|__|__||__|__|__||__|__|__|__|
	|__|__||__|__|__||__|__|__|__|	☐ Yes ☐ No →	|__|__||__|__|__||__|__|__|__|

GlaxoSmithKline

Protocol (eTrack number) **109810** **Abbreviated Title** **ROTA-036 EXT Y 3**	**Country**	**Center Number**	**Subject Number**	**Treatment Number**

SECTION 7 – Other relevant risk factors:

(specify any family or social history (smoking, diet, drug abuse, occupational hazard) relevant to the SAE):

SECTION 8 – Relevant Concomitant Medications

(include details of any concomitant medication(s) ***which may have contributed to the event****)*

Drug Name (Trade name preferred)	Dose	Unit	Frequency	Route	Taken prior to study?	Date started Day Month Year (DD MMM YY)	Date stopped Day Month Year (DD MMM YY)	Ongoing	Reason for medication
					☐ No ☐ Yes			☐ No ☐ Yes	
					☐ No ☐ Yes			☐ No ☐ Yes	
					☐ No ☐ Yes			☐ No ☐ Yes	
					☐ No ☐ Yes			☐ No ☐ Yes	

SECTION 9 – Details of investigational product(s)

Vaccine name (in case of multiple vaccination, please specify if vaccines were administered mixed or separately)	Dose N°	Lot N°	Route / site	Date of administration Day Month Year (DD MMM YY)

Was treatment blind broken at investigational site? ☐ No ☐ Yes ☐ Not applicable

GlaxoSmithKline

Protocol (eTrack number) 109810 Abbreviated Title ROTA-036 EXT Y 3	Country	Center Number	Subject Number	Treatment Number
	_____	|__|__|__|__|__|__|	|__|__|__|__|__|__|	|__|__|__|__|__|

SECTION 10 – Details of relevant assessments	*(provide details of any other tests/procedures which were carried out to diagnose or confirm the SAE, e.g. laboratory data with units and normal range)*

SECTION 11 – Narrative remarks (description of signs/symptoms and details of **TREATMENT** given for SAE)

Protocol (eTrack number) **109810** **Abbreviated Title** **ROTA-036 EXT Y 3**	**Country** _____	**Center Number** |__|__|__|__|__|__|	**Subject Number** |__|__|__|__|__|__|	**Treatment Number** |__|__|__|__|__|

SECTION 12 – SAE additional / follow-up information *(use this page to provide any additional details on the SAE not already captured on the previous pages)*

Investigator's Signature	1. Initial report	2. First follow-up	3. Second follow-up	4. Third follow-up
Date (Day Month Year)	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|
Investigator's Name (print)				

109810 (ROTA-036 EXT Y3)

Protocol	Previous study	Tracking Document Reason for non participation	Center Number
109810	**102247 (Rota-036)**		|__|__|__|__|__|__|

Previous Subject Number	Date of Birth *(day month year)*	**Reason for non participation**	Date of Contact *(day month year)*
|_|_|_|_|_|_|	|_|_||_|_|_||_|_|_|_|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: _____________________ [2] ☐ Subject lost to follow-up or not reached [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event Please specify: ___________________ ☐ Other Please specify: ____________________ [4] ☐ Subject died on |_|_| |_|_|_| |_|_|_|_|	|_|_||_|_|_||_|_|_|_|
|_|_|_|_|_|_|	|_|_||_|_|_||_|_|_|_|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: _____________________ [2] ☐ Subject lost to follow-up or not reached [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event Please specify: ___________________ ☐ Other Please specify: ____________________ [4] ☐ Subject died on |_|_| |_|_|_| |_|_|_|_|	|_|_||_|_|_||_|_|_|_|
|_|_|_|_|_|_|	|_|_||_|_|_||_|_|_|_|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: _____________________ [2] ☐ Subject lost to follow-up or not reached [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event Please specify: ___________________ ☐ Other Please specify: ____________________ [4] ☐ Subject died on |_|_| |_|_|_| |_|_|_|_|	|_|_||_|_|_||_|_|_|_|
|_|_|_|_|_|_|	|_|_||_|_|_||_|_|_|_|	[1] ☐ Subject not eligible -Please specify criteria that are not fullfilled: _____________________ [2] ☐ Subject lost to follow-up or not reached [3] ☐ Subject eligible but not willing to participate due to: ☐ Adverse event(s), or serious adverse event Please specify: ___________________ ☐ Other Please specify: ____________________ [4] ☐ Subject died on |_|_| |_|_|_| |_|_|_|_|	|_|_||_|_|_||_|_|_|_|

Investigator name (PRINT name)	**Signature**:	**Date:** *(day month year)*
		|_|_| |_|_|_| |_|_|_|_|

Confidential - Version 12.3 – January 31, 2007

List of Independent Ethics Committees

Independent Ethics Committees

Centre Number(s)*	Ethics Review Body	Location
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland
[redacted]	[redacted] Finland	Finland

* GSK Biologicals assigned center number

Representative written information for patient and sample consent forms

INFORMED CONSENT AGREEMENT FOR SUBJECTS IN THE THIRD EFFICACY FOLLOW-UP

Study Identification: ROTA-036 EXT Y3 (109810)

Study Title: A phase IIIb study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247).

Version Number: Version 1 Date: 29/11/2006

Company Name: GlaxoSmithKline Biologicals S.A.

Subject Identification: _____

This document should be presented to the Legally Acceptable Representative in full; no page(s) or section(s) should be omitted. The document contents will be mailed to the Legally Acceptable Representative.

What does giving consent for this study mean?

Consent means agreeing to take part in this clinical research study. You have the right to decide if you want your child/ ward to take part in this study or not. Please take time to read the following information carefully and discuss it if you wish with friends, relatives and your personal doctor. If there is anything that is not clear or if you would like more information, you can ask the study doctor. Details of the study doctor have been provided in this document.

Dear Parent or Guardian:

Your child/ ward was part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals. Your child/ ward has already received two doses of the HRV vaccine or placebo by mouth, two months apart.

The parents/ guardian of the children who were followed up to 24 months of age will also be invited to participate in this study. This follow-up will be conducted in Finland.

Your child/ ward has been followed up to 24 months of age and we would like to continue following your child/ ward for a third year follow-up (until the age of 36 months). Your child/ ward will not be given any vaccination during this period.

The study doctor/ study personnel will contact you once every two weeks until the end of the study period through a telephone call or by sending you a text message on your mobile phone. The intended duration of the study for your child/ ward will be approximately six months. No additional blood samples will be taken from your child/ ward.

Once you give consent to this study, you will be asked questions by the study doctor regarding any diarrheal episode, intussuception and death that might have occurred between the end of the second follow-up period up to the start of the study.

This third year follow-up is being conducted as we want to check if your child/ ward experiences any diarrhoeal episodes even after receiving the vaccination. To record any episode, a diary card will be provided to you. This diary card should be completed daily to record the symptoms (axillary/ rectal temperature, number of vomiting episodes and number of looser than normal stools passed by your child/ ward and behavioural symptoms) until two days after looser stools and/ or vomiting have disappeared.

You will have to collect your child's/ ward's stool sample using the materials that will be provided to you. You will be required to inform the study personnel (when he/ she contacts you bi-weekly) of any diarrheal episodes that your child/ ward had experienced in the past two weeks. If there has been any diarrheal episode, you will be required to freeze the stool sample in the home freezer. The study personnel will then make a home visit to collect the stool sample and the diary card from you. If the diarrheal episode is still ongoing when the study personnel comes for sample collection, then you can mail the diary card to the study centre later.

Collected stool samples may be stored and used for purposes for up to 15 years related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably. Samples will not be labelled with information that directly identifies your child/ward but will be coded with your child/ward's study subject number.

Collected samples may also be anonymized (meaning that the link between your child/ward and the sample will be destroyed) to be used for other research purposes.

There will be no charge for study-related doctor visits, examinations and laboratory tests.

If you decide to let your child/ward participate in the study, the study doctor and staff will collect medical and personal information about your child/ward as part of doing the study. People who work for or with GSK, and others like the independent ethics committee or the institutional review board (IEC/ IRB) for the study or regulatory authorities responsible for approving medicines, will have access to this information at the site in order to check that the study is done properly. GSK staffs who see this information at the site will keep it confidential.

You may ask questions about this study or about your rights as a parent/ guardian in a research study. If you have any questions, please contact:

Name of investigator:

Address of investigator:

Telephone number of investigator:

Fax number of investigator:

Informed Consent Form **CONFIDENTIAL** **Subject ID**_____
Study Identification: 109810 (Ext- Rota-036)

Supplemental Consent statement

_____

I, (Printed name of the Parent/ Guardian of the subject.)

- confirm that I have read the written information (or have had the information read to me) for study 109810 (Ext-Rota-036), Supplemental ICF dated 29/11/2006, 3 pages .
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data to authorised persons described in the information sheet
- have been given time and opportunity to consider the participation of my child/ ward part in this study.

Tick as appropriate (this decision will not affect your child's/ ward's ability to enter the study):

I agree that my child's/ ward's primary health care physician will be notified of my child/ ward's participation in this study. **Yes** **No**

I agree to let my child/ ward take part in this study.

Name of the Subject _____

***Signature of Legal Representative** _____ **Date:** _____
DD/ MM/ YY

***Printed name of Legal Representative** _____

Signature of Person conducting Consent _____ **Date:** _____
DD/ MM/ YY

Printed Name of Person conducting Consent _____

List of investigators and other important participants in the study, contact information and number and distribution of subjects

Investigator's name	Center number*	Number of subjects enrolled per center (% of enrollment)	Investigational site (institution /hospital)	Location complete address)	Phone number Fax number
[redacted]	[redacted]	189 (11.7)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	148 (9.2)	institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	107 (6.6)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted] (former PI: [redacted])	[redacted]	112 (6.9)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	60 (3.7)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted] (former PI: [redacted])	[redacted]	72 (4.5)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted] (former PI: [redacted])	[redacted]	80 (5.0)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	148 (9.2)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	96 (6.0)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]

Investigator's name	Center number*	Number of subjects enrolled per center (% of enrollment)	Investigational site (institution /hospital)	Location complete address)	Phone number Fax number
[redacted]	[redacted]	88 (5.5)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	77 (4.8)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	107 (6.6)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	63 (3.9)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	82 (5.1)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	71 (4.4)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	52 (3.2)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]
[redacted]	[redacted]	61 (3.8)	Institution: [redacted]	[redacted] FINLAND	Phone: [redacted] Fax: [redacted]

* GSK Biologicals' assigned center number

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals

Global Clinical Research and Development

Investigator Approval Page

Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

Study: Rota-036 EXT Y3 (109810) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator: _____

Affiliation /investigational centre: _____

Signature of Investigator: _____

Date: _____

For internal use only
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1a7fe35a92a4743b967abae0e6acf743 1.0 19/10/2009

GlaxoSmithKline Biologicals
Global Clinical Research and Development

Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.

Study: Rota-036 EXT Y3 (109810) Development Phase: IIIb

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: MD, Ph.D.
Medical Director
GlaxoSmithKline Biologicals, Finland

Signature: _____

Date: _____

For internal use only
----------Checksum----------!Ver.!Created On
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a8e330e5e358d02e8615317c23735f38 1.0 07/12/2009
e378b9520b6c0afec13f0d535d5b2e34 1.0 11/11/2009
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da45535f1f13c4d2d3a0cc710151c596 1.0 19/10/2009
34460fb3f026d95bb44ea6323096030c 1.0 07/12/2009
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a0ad0e7d0ccb8046eef983de943e5881 1.0 07/12/2009
582733088159718a9fd15219f1926cfe 1.1 08/12/2009
1a7fe35a92a4743b967abae0e6acf743 1.0 19/10/2009

Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable

Randomisation List

The Rota-036 EXT year 3 follow up study is an open study. The randomisation list for the same was generated after the completion of the analysis of Rota-036 (102247) study.

Audit Certificates

Not applicable.

Documentation of statistical methods

Refer to Section 4.11 of the report.

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not applicable.

Publications based on the study

Not applicable.

Important publications referenced in the report

Individual Listings

NOTES TO APPENDIX TABLES

The following abbreviations are common throughout the Appendix tables:

Sub. No.		:	Subject number
Eli MA		:	Eligibility (MA: Main Analysis)
	E	:	Eliminated from reactogenicity and immunogenicity analyses
	I	:	Eliminated from immunogenicity analysis
	MC	:	Missing Confirmed
	N	:	No
	Y	:	Yes
	NA	:	Not Applicable

Abbreviations which are unique to a particular appendix are presented below.

Appendix Table IA - Individual subject data: Elimination codes

Elim Codes : Elimination codes

Appendix Table I.B - Individual subject data: Demography

Sex		:	Sex
	F	:	Female
	M	:	Male
Center		:	Study center

Appendix Table ICi - Individual subject data: Dates of Birth - vaccination - sampling - visits

Dates of vaccine administration,
Dates of sampling,
Dates of visits

VIS ND	:	Visit Not Done (the subject did not come)
VAC ND	:	Study vaccine administration not done
ND	:	Not Done

Appendix Table ICii - Individual subject data: Reason for visit not done

Reason		:	Reason for visit not done
	AEX	:	Non serious adverse event
	SAE	:	Serious adverse event
	OTH	:	Other
	SAM	:	Same reason and decision as previous visit

Appendix Table ID - Individual subject data: General medical history - Physical examination

Status

PAST	:	Medical history no more present at the physical examination
CURRENT	:	Medical history present at the physical examination
Both	:	Past and current

Appendix Table IE - Individual subject data: CONCLUSION

Elim Crit		:	Did any elimination criteria become applicable during the study?
	Y	:	Yes
	N	:	No
Link to AE		:	Is the withdrawal of the subject linked to an adverse event ?
	Yes	:	
	No	:	
Date of last contact			Date when last information was collected on subject's condition
Good Condition?			Was the subject in good condition at date of last contact?
SAE?		:	Did the subject experience any Serious Adverse Event during the
		:	study?
	Y	:	Yes
	N		No
Nb of SAE		:	Total number of SAE's recorded in SAE report.
Preg		:	Did the subject become pregnant during the study / since the end of the active phase?

Appendix Table IEii - Individual subject data: Subjects whose the code has been broken

Broken date	:	Unblinding treatment date

Appendix Table IEii - Individual subject data: Extensive safety follow-up

Contact date		:	Date of study conclusion extended safety follow-up contact
Sub Cont		:	Was the subject/subject's parents/guardian contacted after the end of the active phase?
Reason		:	Reason for not being contacted:
	Consent withdrawal / Lost to follow-up		
Non-Serious AE?		:	Did the subject experience any study relevant non-serious adverse event(s) since the end of the active phase?

Serious AE ?		:	Did the subject experience any serious adverse event(s) since the end of the active phase
	YES		
	NO		
	Subjects could not be contacted		
Other vaccine		:	Has the subject received any other investigational and/or non-registered vaccine and/or drug since the end of the active phase?
Other vaccine spec		:	Specification of the vaccine
Pregnant		:	Has the subject become pregnant since the end of the active phase?
	YES	:	Yes
	NO	:	No
	NA	:	Not applicable

Appendix table IF - Individual subject data : Notes RDE (sticky notes)

Tbl. Note			
	3	:	Sticky notes
	2	:	Notes data
	1	:	Force validation
Act		:	Activity
Scr Nb		:	Screen number
Screen		:	Screen name
Seq Nb		:	Sequence number
Note		:	Description of the note

Appendix Table IG - Individual subject data: Vaccination procedure for each subject: list of the administered vaccines and all related information

Trt. No.		:	Treatment number
According to Prot?		:	Is of the study vaccine be administered according to protocol in terms of side/site/route?
Injection?		:	Vaccine administration
Type of vacc.			
	1	:	Study vaccine not administered according to protocol: wrong side/site/route or replacement or wrong vial number
	2	:	Study vaccine planned but not administered for a given visit
	3	:	Administration of a study vaccine not planned in the group
Eff Vial Number		:	Effective vial number administered

Appendix Table IH - Individual subject data : Smoking history

Smoke now?		:	Does the subject smoke on a regular basis?
What?		:	What does the subject smoke?
	CIGARETTES		
	CIGARS		
	PIPE		
	CIGARILLOS		
Daily Average		:	How many cigarettes, cigars,… does the subject smoke on average?
	<= 10 DAILY		
	11-20 DAILY		
	21-40 DAILY		
	> 40 DAILY		
Start Date		:	Specification of the year the subject started smoking
Smoke past?		:	Did the subject smoke on a regular basis in the past?
Stop Date		:	Specification of the year the subject quit smoking

Appendix Table II - Individual subject data: Reason for vaccine not administered

Adm?		:	Study vaccine administration
	N	:	Not administered
	R	:	Replacement
	S	:	Study vaccine
	W	:	Wrong vial number
Reason		:	Reason why the study vaccine was not administered:
	SAE	:	Serious adverse event
	AEX	:	Non serious adverse event
	OTH	:	Other

Appendix Table IJ - Individual subject data: Reason for non-Eligibility

Eligib.		:	Did the subject meet all the entry criteria?
	No	:	Some inclusion /exclusion criteria are not met
Study vacc.			
	Yes	:	The subject received at least one dose of study vaccine (study vaccine, Replacement or Wrong vial number)
	No	:	No vaccine received
Criterion number		:	Inclusion OR exclusion criteria number the subject failed
Reason of inclusion and exclusion criteria		:	Description of the criterion number: label from codelist or ‘Cfr. description in CRF’

Appendix table IK - Individual subject data : Tracking Document Booster or Long Term Follow-up

Prev_sub		:	Previous PID number
Origin		:	Origin of the information
	Track.Doc	:	From TRACKDOC of the current study
	Demog	:	From DEMOG of the current study
	Err.Track	:	Inconsistensy between demog and trackdoc
	Prev.Study	:	From FU in Previous study
	No Track	:	Subject from primary without information
DOB		:	Date of birth
Crit_nb		:	Criteria number of the reason for non participation into an extension study
	1		
	2		
	3		
	4		
Comment for non eligibility		:	If the criteria for non participation into an extension study is 'Subject not eligible -Please specify criteria that are not fulfilled'?
Crit Description	-Subject not eligible -Please specify criteria that are not fulfilled -Subject lost to follow-up or not reached -Subject eligible but not willing to participate due to -Subject died		Label of the criteria number
Due to AE?		:	If subject is eligible but not willing to participate due to Adverse events, or Serious adverse event
	Y	:	Yes
	N	:	No
Due to Other?		:	If subject is eligible but not willing to participate due to Other reason that Adverse events, or Serious adverse event
	Y	:	Yes
	N	:	No

Appendix Table IIA - Individual subject data: Solicited local adverse events

L?		:	Has the subject experienced any local symptoms?
	U	:	Information not available
	NA	:	Not Applicable (when the study vaccine was not administered)
	N	:	No
	Y	:	Yes
	M	:	Missing

VACC CODE		:	Vaccine code (corresponding vaccine label presented on the first page of Appendix Table IIA)
VA		:	Vaccine administration
	N	:	Not administered
	R	:	Replacement
	S	:	Study vaccine
	W	:	Wrong vial number
PA		:	Pain (empty or scored from 0 to 3)
RE		:	Redness (greatest diameter)
SW		:	Swelling (greatest diameter)
IN		:	Induration (greatest diameter)
EC		:	Ecchymosis (greatest diameter)
EXP		:	Has the subject experienced some symptoms?
	Y	:	Yes
	N	:	No
MA_TYPE		:	Medical advice sought for the symptom
	ER	:	Emergency room
	HO	:	Hospitalization
	MD	:	Medical doctor
O?		:	Ongoing at the end of the solicited follow-up period?
	Y	:	Yes
	N	:	No
Last day		:	Date of the last day of symptom if it was ongoing after the solicited follow-up period

Appendix table IIB - Individual subject data: Solicited general adverse events

G?		:	Has the subject experienced any general symptoms?
	U	:	Information not available
	NA	:	Not Applicable (when the study vaccine was not administered)
	N	:	No
	Y	:	Yes
	M	:	Missing
AC		:	General aches (empty or scored from 0 to 3)
AR		:	Arthralgia (empty or scored from 0 to 3)
DA		:	Diarrhoea (empty or scored from 0 to 3)
DR		:	Drowsiness (empty or scored from 0 to 3)
FA		:	Fatigue (empty or scored from 0 to 3)
FE		:	Fever = Body temperature in °Cs or °Fs
FU		:	Fussiness (empty or scored from 0 to 3)
GI		:	Gastrointestinal symptoms (empty or scored from 0 to 3)
HE		:	Headache (empty or scored from 0 to 3)
IR		:	Irritability/fussiness (empty or scored from 0 to 3)
LO		:	Loss of appetite (empty or scored from 0 to 3)
MA		:	Malaise (empty or scored from 0 to 3)
MY		:	Myalgia (empty or scored from 0 to 3)

NA		:	Nausea (empty or scored from 0 to 3)
SL		:	Sleeping less than usual (empty or scored from 0 to 3)
SH		:	Shivering (empty or scored from 0 to 3)
SW		:	Sweating (empty or scored from 0 to 3)
UC		:	Unusual crying (empty or scored from 0 to 3)
VO		:	Vomiting (empty or scored from 0 to 3)
TE		:	Temperature = Body temperature in °Cs or °Fs
	RTE	:	Route (for body temperature recording)
	O	:	Oral
	A	:	Axillary
	R	:	Rectal
	T	:	Tympanic
	X	:	Tympanic oral
	Y	:	Tympanic rectal
	Rte Pre	:	Route for pre-vaccination temperature recording
	Pre Vac	:	Pre-vaccination temperature
EXP		:	Symptom experienced
Caus		:	Causality
MA TYPE		:	Medical advice sought for the symptom
	ER	:	Emergency room
	HO	:	Hospitalization
	MD	:	Medical doctor
O?		:	Ongoing at the end of the solicited follow-up period?
	Y	:	Yes
	N	:	No
Last day		:	Date of the last day of symptom if it was ongoing after the solicited follow-up period

Appendix table IIC - Individual subject data: Unsolicited Adverse Event

Verbatim	:	Description of experience as recorded in the case report form
Keyword (MedDRA)	:	Specific identification terminology linked to MedDRA classification codes
LLT MedDRA code	:	Lower Level Term Code for MedDRA, Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym. (All PTs have an identical LLT).
Preferred term	:	Medical term assigned to the keyword/verbatim, Represents a single medical concept
SOC code	:	Primary System Organ Class code: Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose
Chro	:	Chronic illness
Pr Do	:	Study vaccine dose given prior to the adverse event
M?	:	Medical advice sought for the symptom
Type	:	Type of medical advice
ER	:	Emergency room
HO	:	Hospitalization

	MD	:	Medical doctor
Caus		:	Reasonable possibility that the AE have been caused by the investigational product?
Start date		:	Date of onset of adverse event
Imm Pst Vac		:	Adverse event starting during immediate post-vaccination period
Day onset		:	Number of days since last study vaccine dose
End date		:	Date of end of adverse event
Dur (d)		:	Duration (days) of adverse event
Int		:	Maximum intensity
	1	:	Mild
	2	:	Moderate
	3	:	Severe
L/G		:	Local or general symptom
Out		:	Outcome
	1	:	Recovered/Resolved
	2	:	Recovering/Resolving
	3	:	Not recovered/Not resolved
	4	:	Recovered with sequelae/Resolved with sequelae
	5	:	Died
Vacc Code		:	Vaccine code (corresponding vaccine label presented on the first page of Appendix Tables IIC)
Ser		:	Serious adverse event

Appendix tables IIDi - Individual subject data: Medication

Prev dose		:	Previous study vaccine dose
Rel. day of onset		:	Day of onset of medication, relative to previous study vaccine dose
Start date		:	Start date of medication
End date		:	End date of medication
Dur (day)		:	Duration (days) of medication
Trade-Generic name		:	Trade and/or generic name of medication
Medical indication		:	Medical indication for which medication was used
GSK Antibiot		:	Antibiotic
	Y	:	Yes
GSK Antipyr		:	Antipyretic
	Y	:	Yes
Proph		:	Prophylactic medication
	Y	:	Yes

Appendix table IIDii - Individual subject data: Concomitant Vaccination

Trade name	:	Trade name of concomitant vaccine administered
Admin. date	:	Date of administration of concomitant vaccine
Previous vaccination date	:	Date of administration of previous study vaccine dose
Prev dose	:	Previous study vaccine dose
Rel. day of onset	:	Day of onset of concomitant vaccination, relative to date of previous study vaccine dose

Appendix Tables IIE - Individual subject data: Extensive swelling limbs

Vac		: Vaccine administered for which the large swelling reaction is reported
Physexam		: Date of physical examination
Exam		: Was the examination performed by a member of study personnel during the large swelling reaction period?
	Y	: Yes
	N	: No
Ext. Swell Start		: Date when the swelling was first considered to be a large swelling reaction
H. advc		: Number of hours between last vaccination and large swelling reaction, if the swelling occured within 24 hours after vaccination
Pr Do		: Previous dose of vaccination
Day onset		: Number of days between the previous vaccination date and the onset date of large swelling reaction
Sw. size		: Measurement of the greatest diameter of swelling (mm)
Swe Typ		: Type of swelling
	LOC	: local swelling around injection site, not involving adjacent joint
	DIF	: diffuse swelling, not involving adjacent joint
	ADJ	: swelling, involving adjacent joint
Circum swo		: Circumference of swollen limb (at the site of max swelling) (mm)
Circum opp		: Circumference of the opposite limb (at the same level) (mm)
Val temp		: Temperature (maximum temperature if temperature has been taken more than once a day)
Rout		: Temperature measurement route
	A	: axilllary
	O	: oral
	R	:: Rectal
	X	tympanic
Red		: Symptom of redness occurring during the large swelling reaction
Red Dia		: Largest diameter of redness (mm)
Ind		: Symptom of induration occurring during the large swelling reaction
Ind Dia		: Largest diameter of induration (mm)
Pain		: Symptom of pain occurring during the large swelling reaction
Pain Int		: Pain intensity (at administration site)
	1	: Minor reaction to touch
	2	: cries/ protests on touch
	3	: cries when limb is moved / spontaneously painful
Func Imp		: Symptom of functional impairment occurring during the large swelling reaction
Imp Int		: Functional impairment intensity
	1	: easily tolerated, causing minimal discomfort and not interfering with everyday activities
	2	: sufficiently discomforting to interfere with normal everyday
	3	: activities prevents normal everyday activities

Ext. Swell. end		: Last date when the swelling was still considered to be large swelling reaction
H. dura		: Duration in hours, if the large swelling reaction lasted for less than 24 hours.
Out		: Outcome of the large swelling reaction
	1	: recovered/resolved
	2	: recovering/resolving
	3	: not recoverd / not resolved
	4	: recovered with sequelae / resolved with sequelae
Alt Expl		: Is there an alternative explanation for the swelling?
	Y	: Yes
	N	: No
Explanat		: Explanation of an alternative for the swelling

Appendix table IIIA - Individual subject data: IMMUNOGENICITY

cut	:	Cut-off of the laboratory assay
GSKBIO	:	GlaxoSmithKline Biologicals
AP	:	Absence of parallelism
BS ND	:	Blood sampling not done
IR	:	Invalid result
QNS	:	Quantity of serum not sufficient
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IIIB - Individual subject data: CMI

QCNF	:	Quality Criteria Not Fulfilled
TP	:	Technical Problem
NM	:	No Material
ND	:	Not Done
NR	:	Not recorded
IR	:	Invalid results
BSNA	:	Blood Sample Not Available

Appendix table IVA - Individual subject data: Haematology

cut	:	Cut-off of the laboratory assay
INVESTIG	:	Investigator
VIS ND	:	Visit not done
ND	:	Not done
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination

PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IVB - Individual subject data: Biochemistry

cut	:	Cut-off of the laboratory assay
INVESTIG		Investigator
VIS ND	:	Visit not done
ND	:	Not done
Blank	:	Blood sample not available or test not requested
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

Appendix table IVC - Individual subject data: Urinology

cut	:	Cut-off of the laboratory assay
INVESTIG	:	Investigator
SBCODE/RES	:	SmithKline Beecham code/Result
VIS ND	:	Visit not done
ND	:	Not done
PRE	:	Pre-vaccination
PI	:	Post-vaccination 1
PII	:	Post-vaccination 2
PIII	:	Post-vaccination 3

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 ***GSK Clinical Study Register****.*

CRF /eCRFs for deaths, other SAEs and withdrawals due to adverse events

GlaxoSmithKline

Study Reporting and Analysis Plan Approval

Title:	A phase IIIb open study to assess the long-term efficacy and safety of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine approximately three years after vaccination in healthy infants aged 6-12 weeks at the time of first vaccination in the Rota-036 study (eTrack No.102247) in Finland.
eTrack study number	109810
eTrack abbreviated title	ROTA-036 EXT Y3
Scope:	All data pertaining to the above study
Date:	13-Mar-08
Co-ordinating author:	[redacted]
Other author(s):	

Approved by:

Director, Worldwide Clinical Development, Rotavirus Vaccines	[redacted]	Signature	dd-mmm-yyyy
Senior Manager, Clinical Management	[redacted]	Signature	dd-mmm-yyyy
Project Statistician	[redacted]	Signature	dd-mmm-yyyy
Director, Statistical Manager	[redacted]	Signature	dd-mmm-yyyy

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LIST OF TABLES AND FIGURES

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
CI	Confidence Interval
GE	Gastroenteritis
GSK	GlaxoSmithKline
HRV	Human Rotavirus
IS	Intussusception
RV	Rotavirus
SAE	Serious Adverse Event

1. LIST OF AMENDMENTS TO THE RAP

Date	Description
05-Mar-08	First version
13-Mar-08	• Figure 1 & 2 (i.e. Figure for the Distribution of Vesikari and Clark score for RV GE episodes) have been updated. The update is with respect to the Y-axis showing percentage instead of number. • Table R2 (i.e. Number of mortalities (Total cohort)) will include both the retrospective & prospective follow-up data instead of separate follow ups. • CTRS table for (Number (%) of subjects with IS and fatalities) is not needed as it is available from CTRS table for (Number (%) of subjects with serious adverse events). Hence this table has been deleted.

2. INTRODUCTION

This Study Reporting and Analysis Plan summarize the 109810 (ROTA-036 EXT Y3) study features, as per protocol dated 29 November 2006 and the planned statistical analysis (Sections 3). The list of tables and listings to be produced in the statistical report is available in annex 1.

3. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

3.1. Primary Endpoints

- Occurrence of any RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.

3.2. Secondary Endpoints

Efficacy endpoints:

The endpoints during the study period for the long-term follow-up are as follows:

- Occurrence of severe RV GE caused by the wild-type RV strains during the study period for the long-term follow-up
- Occurrence of any and severe RV GE caused by the wild-type RV strain of serotype G1.
- Occurrence of any and severe RV GE due to non-G1 serotypes.
- Occurrence of severe GE.

Safety endpoints:

- Occurrence of mortality and SAEs during the study period for the long-term follow-up.
- Occurrence of mortality and IS during the period from the end of the second follow-up period up to the start of the study.

3.3. Study cohorts to be evaluated

3.3.1. Total cohort

The total cohort will include all subjects who participate in this follow up study with at least one vaccine administration documented in the primary study:

- an efficacy analysis based on the total cohort will include all subjects for whom efficacy follow-up data are available.

3.3.2. According-To-Protocol (ATP) cohort for analysis of safety

Not applicable.

3.3.3. ATP cohort for analysis of immunogenicity

Not applicable.

3.3.4. ATP cohort for analysis of efficacy

The ATP cohort for efficacy will include all subjects from the ATP efficacy cohort of the primary study who have entered into the efficacy surveillance period.

3.4. Derived and transformed data

Efficacy

An episode of GE will be classified positive for RV caused by the circulating wild-type RV strains if RV other than vaccine strain is identified in a stool sample collected during

the episode. GE episode without stool sample/result available will not be considered in the analysis as a RV GE episode.

3.5. Data presentation description

Display Table	Parameters	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	p-value	3
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2

3.6. Group description

The following groups will be used for the statistical analyses.

Study	Group order in tables	Group label in tables (8 characters only)
109810	1	HRV
	2	Placebo

3.7. Final analyses

3.7.1. Analysis of demographics/baseline characteristics

The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group. The mean, range and standard deviation of age in year will be calculated per group. The racial and gender composition will be tabulated

3.7.2. Analysis of efficacy

Vaccine efficacy will be calculated, with their 95% CI against:

- any and severe RV GE caused by the circulating wild-type RV strains during the study period for the long-term follow-up.
- any and severe RV GE due to G1 serotype caused by the circulating wild-type RV strains during the study period for the long-term follow-up.
- any and severe RV GE due to non-G1 serotypes during the study period for the long-term follow-up.
- severe GE during the study period for the long-term follow-up.

Exploratory efficacy analysis based on history of GE in the primary study will be done.

3.7.3. Analysis of immunogenicity

Not applicable.

3.7.4. Analysis of safety

Serious adverse events and mortalities reported during the study follow-up period will be summarized by group. Retrospective death, IS and GE will also be summarised by group.

4. CHANGE FROM PROTOCOL

None

5. ANNEX 1: INDIVIDUAL LISTINGS AND TEMPLATE OF TABLES

5.1. Individual listings for the final analysis

Appendix Table I.A - Elimination codes

Appendix Table I.B - Demography

Appendix Table I.Ci - Dates of birth, Informed consent, Contact

Appendix Table I.Cii - Reason for visit not done

Appendix Table I.D – General medical history

Appendix Table I.Ei – Study Conclusion

Appendix Table II.Cii - Unsolicited adverse events during the study period

Appendix Table II.Ciii- Serious adverse events during the study period

Appendix Table II.Di - Medication

Appendix Table IV.A - Gastroenteritis stool collection results

Appendix Table VA – Detailed information of GE episodes

5.2. List of tables for the final analysis

5.2.1. For Demographics Analysis:

TABLE # in reference of section 5.3	Table Title	Final Analysis	Macro
Table D 1	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for efficacy with reasons for exclusion in the follow up period	CR	%ELIMLIST
Table D 2	Number of subjects by center (Total cohort)	CR	%CENTER
Table D 3	Summary of demographic characteristics (Total cohort)	CR	%DEMOGRA
Table D 3	Summary of demographic characteristics (ATP cohort for efficacy)	ST	%DEMOGRA
Table D 4	Minimum and maximum activity dates (Total cohort)	WT	%DATE
Table D 5	Number of subjects entered, completed and withdrawn with reason for withdrawal - (Total cohort)	CR	%DROP_SUM
Table CTRS 1	Demography for CTRS - Total cohort	CTRS	%CTR_DEMOG

CR = Within the clinical report
ST = As a supplementary table or figure of the clinical report

WT = As a working table or figure (not included in the clinical report)

5.2.2. For Safety Analysis:

The following tables will be generated:

TABLE # in reference of annex 1	Table Title	Final Analysis	Macro
Table R 1	Listing of SAEs in the follow up period (Total cohort)	CR	%SAE
Error! Reference source not found.	Number of mortalities (Total cohort)	CR	
Table R 2	Number of IS from the end of the second follow up period up to the start of the study –(Total cohort)	CR	
Table R 2	Number of GE from the end of the second follow up period up to the start of the study- (Total cohort)	CR	
Table CTRS 2	Number (%) of subjects with serious adverse events (Total cohort)	CTRS	%CTR_SAE

CR= Within the clinical report
ST = As a supplementary table or figure of the clinical report
WT = As a working table or figure (not included in the clinical report)
CTRS = table for use in the clinical trial registry summary

5.2.3 For Efficacy Analysis

The following tables will be generated:

Table in reference of annex 1	Denomination	Final Analysis	Macro
Table E 1	Percentage of subjects with vaccine virus in stool samples collected in case of GE episode during the follow up period- ATP cohort for efficacy	ST	
Table E 2	Percentage of subjects who reported GE episodes and RV GE episodes during the follow up period- ATP cohort for efficacy	CR	%FREQ_DIS
Table E 3	Percentage of GE episodes with no available stool results during the follow up period- ATP cohort for efficacy	ST	%FREQ_DIS
Table E 4	Number of GE episodes and RV GE episodes reported during the follow up period, by severity using the 20-point Vesikari scale - ATP cohort for efficacy	CR	%FREQ_DIS
Table E 5	Number of GE episodes and RV GE episodes reported during the follow up period, by severity using the 24-point Clark scale - ATP cohort for efficacy	ST	%FREQ_DIS

Table E 6	Percentage of subjects with RV GE episodes reported during the follow up period by G serotype and P genotype - ATP cohort for efficacy	ST	%FREQ_ DIS
Table E 7	Number of RV GE episodes reported during the follow up period, by G serotype and P genotype- ATP cohort for efficacy	ST	%FREQ_ DIS
Table E 8	Characteristics (based on Vesikari scale) of RV GE episodes reported during the follow up period, by main serotype and overall (ATP cohort for efficacy)	ST	%FREQ_ DIS
Table E 9	Characteristics (based on Vesikari scale) of RV GE episodes reported during the follow up period, by main serotype and overall (ATP cohort for efficacy)	ST	%FREQ_ DIS
Table E 10	Duration (in years) of follow-up period – ATP cohort for efficacy	ST	%FREQ_ DIS
Table E 11	Percentage of subjects reporting any RV GE and efficacy of the vaccine during the follow-up period - ATP cohort for efficacy	CR	%VEBY GRP
Table E 11	Percentage of subjects reporting any RV GE episode by main serotype and efficacy of the vaccine during the follow-up period- ATP cohort for efficacy	CR	%VEBY GRP
Table E 11	Percentage of subjects reporting severe RV GE episode (with a score >=11 in using the 20-point Vesikari scale)and efficacy of the vaccine during the follow up period – ATP cohort for efficacy	ST	%VEBY GRP
Table E 11	Percentage of subjects reporting severe RV GE episode (with a score >=16 in using the 24-point Clark scale)and efficacy of the vaccine during the follow up period – ATP cohort for efficacy	ST	%VEBY GRP
Table E 12	Percentage of subjects reporting severe RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine during the follow-up period - ATP cohort for efficacy	ST	%VEBY GRP
Table E 12	Percentage of subjects reporting severe RV GE episodes (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during the follow-up period, by main serotype - ATP cohort for efficacy	ST	%VEBY GRP
Table E 13	Percentage of subjects reporting severe RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine during the follow-up period - ATP cohort for efficacy	ST	%VEBY GRP
Table E 14	Percentage of subjects reporting severe GE episode (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during the follow-up period-ATP cohort for	CR	%VEBY GRP

	efficacy		
Table E 14	Percentage of subjects reporting RV GE episode with medical attention and efficacy of the vaccine during the follow up period – ATP cohort for efficacy	CR	%VEBY GRP
Table E 14	Percentage of subjects reporting all cause severe GE episodes and efficacy of the vaccine during the follow up period - ATP cohort for efficacy		
Figure 1	Distribution of Vesikari score for RV GE episodes	ST	%Graph_ score_R V_GE
Figure 2	Distribution of Clark score for RV GE episodes	ST	%Graph_ score_R V_GE
Figure 3	Efficacy of the vaccine against RV GE with a score ≥ X on the Vesikari scale during the follow up period-ATP cohort for efficacy	WT	
Figure 4	Efficacy of the vaccine against RV GE with a score ≥ X on the Clark scale during the follow up period-ATP cohort for efficacy	WT	
Table E 15	Efficacy of the vaccine against any RV GE during the follow-up period, by Cox – ATP cohort for efficacy	WT	
Table E 15	Efficacy of the vaccine against any RV GE of main serotype during the follow up period, by Cox	WT	
Table E 16	Percentage of subjects who reported GE episodes and RV GE episodes by Year 1 and Year 2- ATP cohort for efficacy		
Figure 5	The Kaplan Meier curve for any RV GE / any RV GE due to G1 serotype / any RV GE due to non-G1 serotypes during the follow-up period - ATP cohort for efficacy	WT	

#: a complementary analysis based on the total cohort will be provided if more than 5% of the subjects are excluded from the ATP cohort for efficacy. The resulting tables will appear as supplemental tables.

The follow up period considered is from Jan 2007 up to the end of Jun 2007.

5.3. Template of tables

Table D 1 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for efficacy with reasons for exclusion in the follow up period

Title	Total	Percent	HRV	Placebo
Total cohort				
Subjects not entered into the surveillance period of the first efficacy follow-up period (3020)				
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response(3030)				
ATP efficacy cohort				

Percent = percentage of subjects in the considered ATP cohort relative to the Total cohort.
Subjects may have more than one elimination code assigned therefore for each elimination reason n (s) is provided where:
n= number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s= number of subjects with the elimination code assigned
Data source = Appendix table IA

Table D 2 Number of subjects by center (Total cohort)

Center	HRV	Placebo	Total	
	N	N	n	%
[redacted]				

- n = number of subjects included in each group or in total for a given center or for all centers.
- All = sum of all subjects in each group or in total (sum of all groups).
- % = n/All*100
- Center = GSK assigned center number.

Data source = Appendix table I.B

Table D 3 Summary of demographic characteristics (Total cohort)

Characteristics	Parameters or Categories	HRV N=		Placebo N=		Total N=	
		Value or n	%	Value or n	%	Value or n	%
Age(in months at Y3)	Mean						
	SD						
	Median						
	Minimum						
	Maximum						
Gender	Female						
	Male						
Ethnicity	American Hispanic or Latino						
	Not American Hispanic or Latino						
Race	African Heritage / African American						
	American Indian or Alaskan Native						
	Asian-Central/South Asian Heritage						
	Asian-East Asian Heritage						
	Asian-Japanese Heritage						
	Asian-South East Asian Heritage						
	Native Hawaiian or other Pacific Islander						
	White-Arabic/ North African Heritage						
	White-Caucasian / European Heritage						
	Other, Specify						
Height (cm)	Mean						
	SD						
	Median						
Weight (kg)	Mean						
	SD						
	Median						

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD= standard deviation
Age(Y)= age expressed in years
Data source = Appendix table I.B

Table D 4 Minimum and maximum activity dates (Total cohort)

Activity number	Minimum date	Maximum date
10		
15		
20		
25		
30		

Table D 5 Number of subjects entered, completed and withdrawn with reason for withdrawal - (Total cohort)

	Group		
	HRV	Placebo	Total
Number of subjects enrolled			
Number of subjects completed			
Number of subjects withdrawn			
Reasons for withdraw:			
Serious Adverse Event			
Non-serious adverse event			
Protocol violation			
Consent withdrawal (not due to an adverse event)			
Migrated/moved from study area			
Lost to follow-up (subjects with incomplete vaccination course)			
Lost to follow-up (subjects with complete vaccination course)			
Others			

Enrolled = number of subjects who where enrolled in the study
Completed = number of subjects who completed the follow up visit
withdrawn = number of subjects who did not come for the follow up visit
Data source = Appendix table I.E

Table CTRS 1 Demography for CTRS - Total cohort

Number of subjects	**HRV**	**PLACEBO**
Planned, N		
Randomised, N (Total Cohort)		
Completed, n (%)		
Total Number Subjects Withdrawn, n (%)		
Withdrawn due to Adverse Events, n (%)		
Withdrawn due to Lack of Efficacy, n (%)		
Withdrawn for other reasons, n (%)		
Demographics	**HRV**	**PLACEBO**
N (Total Cohort)		
Females:Males		
Mean Age, months (SD)		
White/caucasian, n (%)		

Table R 1 Listing of SAEs in the follow up period (Total cohort)

Group	Pid	Case Id	Age (Month)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
HRV													
Placebo													

HRV = HRV vaccine
Placebo=Placebo
All SAEs occurred during the enrolment phase, the active and extended safety follow-up phases were identified
Age (Month) = Age (month) at SAE onset
Data source = Appendix table II.Ci

Table R 2 Number of mortalities (Total cohort)

HRV (N=)				Placebo (N=)			
n	%	95%CI		n	%	95%CI	
		LL	UL			LL	UL

N=total number of subjects
n/% = number/percentage of subjects died both in the retrospective and prospective follow ups

Table CTRS 2 Number (%) of subjects with serious adverse events (Total cohort)

All SAEs	**HRV N = XXX**	**PLACEBO N =XXX**
Subjects with any SAE(s), n(%) [n related]		
Appetite increased		
Asthma		
Bronchitis		
Crying abnormal		
Eczema		
Fever		
Gastroenteritis		
infection bacterial		
infection viral		
Injury		
Laryngitis		
Meningitis		
otitis media		
Pneumonia		
Seborrhea		
Somnolence		
upper resp tract infection		
All fatal SAEs	HRV N = XXX	PLACEBO N = XXX
Subjects with any SAE(s), n(%) [n related]		

Table E 1 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode during the follow up period- ATP cohort for efficacy

Group	**N**	**n**	**%**	**95%CI**	
				LL	**UL**
(Each group)					

N = number of subjects included in each group
n/% = number/percentage of subjects with vaccine virus in at least one stool sample collected in case of GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
Data Source= Appendix Table V.A

Table E 2 Percentage of subjects who reported GE episodes and RV GE episodes during the follow up period- ATP cohort for efficacy

Event	Total number of episodes reported	HRV n %	Placebo n %
GE	1 2 … Any		
RV GE	1 2 … Any		

N = number of subjects included in each group, for the considered efficacy follow-up period
n/% = number/percentage of subjects reporting the specified total number of episode in the considered efficacy period
Any = number and percentage of subjects reporting at least one specified episode in the considered efficacy period
Data Source = Appendix Table IV.A and V.A

Table E 3 Percentage of GE episodes with no available stool results during the follow up period- ATP cohort for efficacy

Category	HRV n	%	Placebo n	%	Total n	%
No stools collected **Stools collected but no results available** **No stool results available**						

N'= number of GE episodes reported in the considered efficacy period
n/%= number/percentage of GE episodes reported in the considered efficacy period within the specified category
Data Source = Appendix Table V.A

Table E 4 Number of GE episodes and RV GE episodes reported during the follow up period, by severity using the 20-point Vesikari scale - ATP cohort for efficacy

Event	Severity using the 20-point Vesikari scale	HRV n %	Placebo n %
GE	**Mild (1-6)** **Moderate (7-10)** **Severe (≥11)** **Any**		
RV GE	**Mild (1-6)** **Moderate (7-10)** **Severe (≥11)** **Any**	 **-**	

n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported during the considered efficacy period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy period
Data Source = Appendix Table IV.A and V.A

Table E 5 Number of GE episodes and RV GE episodes reported during the follow up period, by severity using the 24-point Clark scale - ATP cohort for efficacy

Event	Severity using Clark scale	HRV n	HRV %	Placebo n	Placebo %
GE	Mild (1-8)				
	Moderate (9-16)				
	Severe (≥17)				
	Unknown				
	Any				
RV GE	Mild (1-8)				
	Moderate (9-16)				
	Severe (≥17)				
	Any				

n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported
Any = any specified symptom reported, regardless of Clark severity scale
Data Source = Appendix Table IV.A,and V.A

Figure 1 Distribution of Vesikari score for RV GE episodes (ATP cohort for efficacy

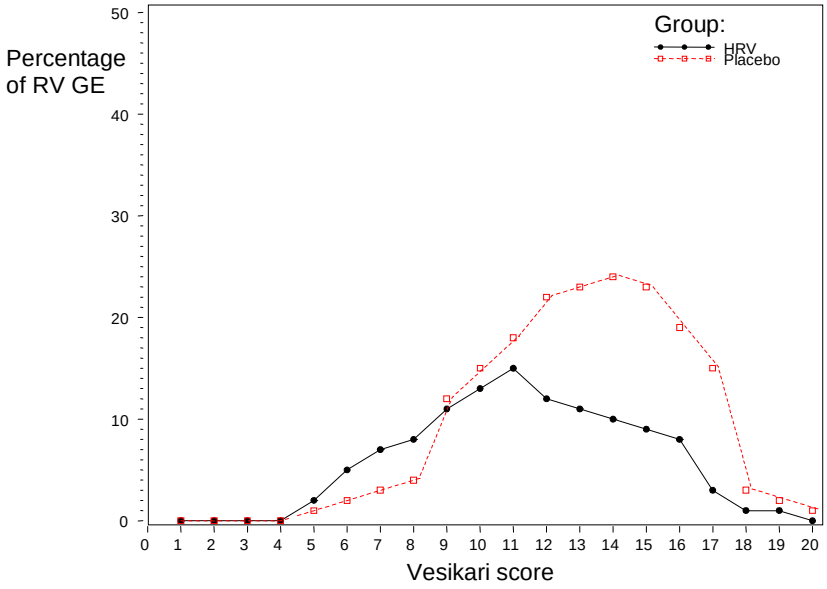


Figure 2 Distribution of Clark score for RV GE episodes (ATP cohort for efficacy

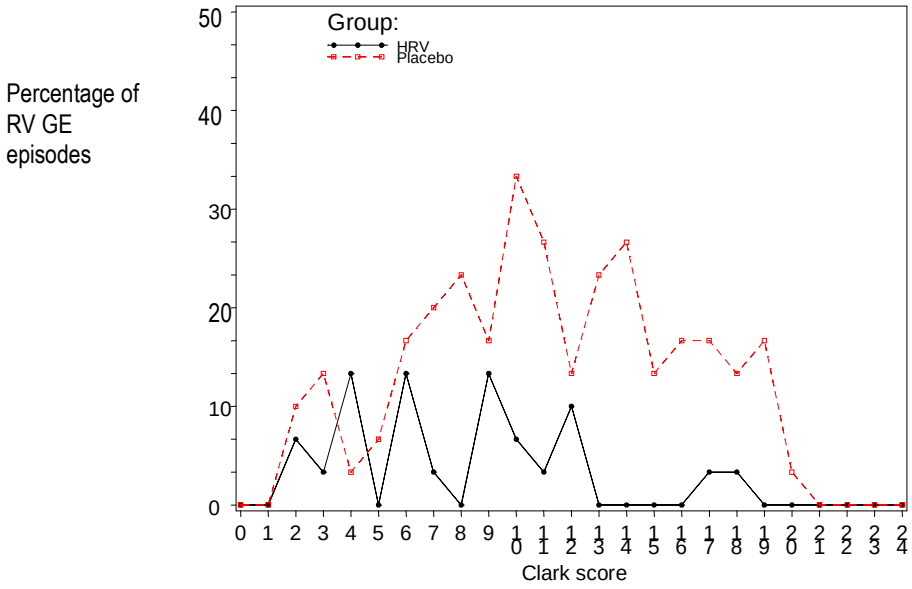


Table E 6 Percentage of subjects with RV GE episodes reported during the follow up period by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV		Placebo	
	n	%	n	%
	N=		N=	
Any				
G1/P8				
G2/P4				
....				

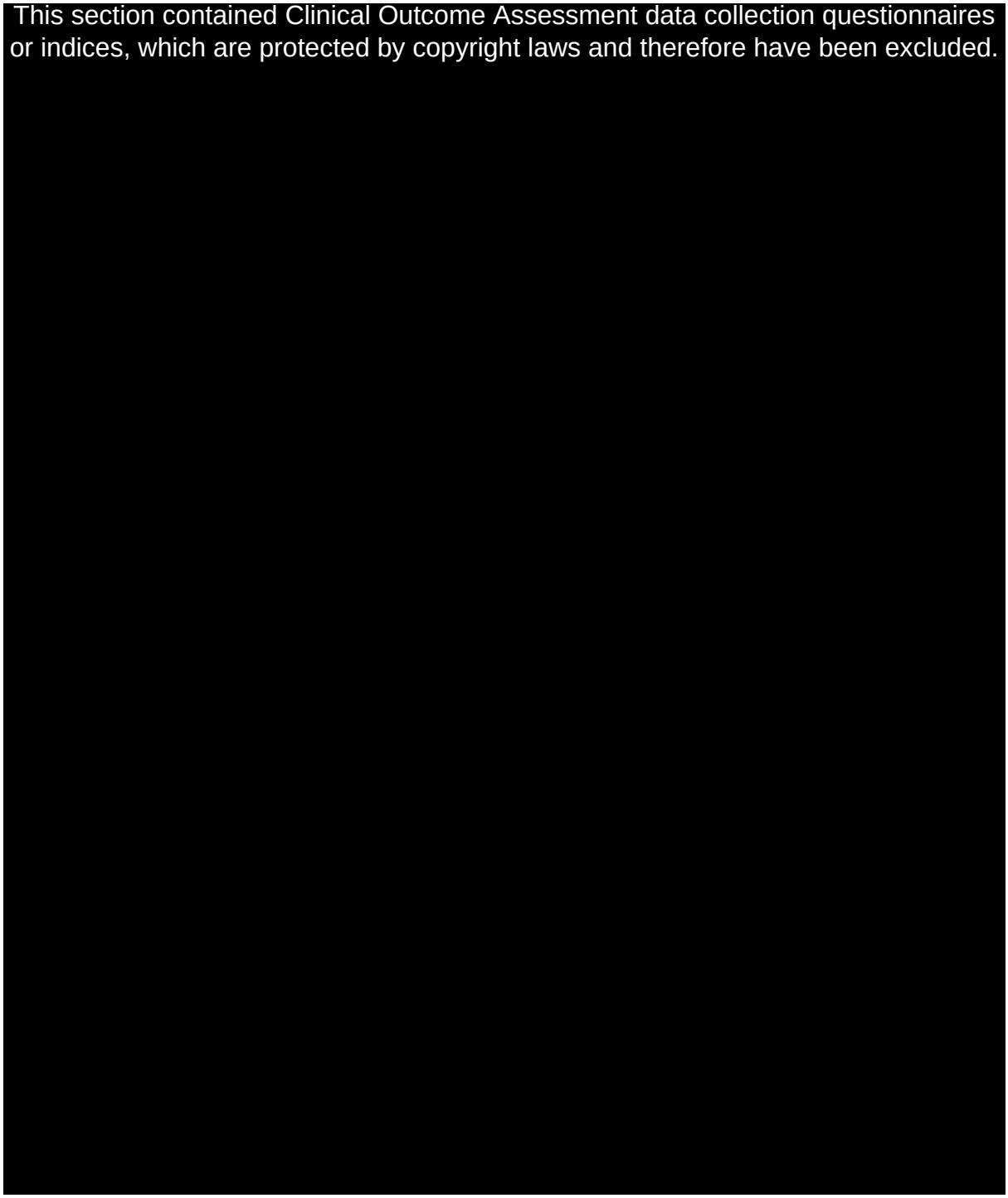
N = number of subjects included in each group, for the considered efficacy period
n/% = number/percentage of subjects reporting at least once the specified serotype in the considered efficacy period
Any = number of subjects reporting at least one severe RV GE episode, whatever the serotype, in the considered efficacy period
Data Source= Appendix Table IVA and V.A

Table E 7 Number of RV GE episodes reported during the follow up period, by G serotype and P genotype- ATP cohort for efficacy

Serotype	HRV (N'=)		Placebo (N'=)	
	n	%	n	%
G1 wild type				
G2				
G4 and G9				
….				

N'= number of RV GE episodes reported in the considered efficacy period
n/%= number/percentage of RV GE episodes reported in the considered efficacy period, by serotype
Data Source= Appendix Table IVA and V.A

Table E 8 Characteristics (based on Vesikari scale) of RV GE episodes reported during the follow up period, by main serotype and overall (ATP cohort for efficacy)



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

Data Source= Appendix Table IVA and V.A

Table E 9 Characteristics (based on Clark scale) of RV GE episodes reported during the follow up period, by main serotype and overall (ATP cohort for efficacy)

Characteristics	Parameters or Categories	HRV N'= 24 Value or n	%	Placebo N'= 94 Value or n	%
Severity Score	Mean SD Median Minimum Maximum				
Duration of looser than normal stools (days)	0 day 1-4 days 5-7 days > 7 days				
Maximum number of looser than normal stools/24 hours	0 2-4 5-7 > 7				
Duration of vomiting (days)	0 - 1 day 2 days 3-5 days > 5 days				
Maximum number of episodes of Vomiting/24 hours	0 1-3 4-6 > 6				
Duration of fever (days)	0 day 1-2 day 3-4 days ≥ 5 days				
Maximum fever reported /24 hours (measured rectally)	< 38.0°C 38.0-38.2°C 38.3-38.7°C ≥ 38.8°C				
Duration of behavioral symptom	0 day 1-2 days 3-4 days ≥ 5 days				
Behavioral symptoms	Behave as usual Irritable/less playful Lethargic/listless Seizures				

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

Table E 10 Duration (in years) of follow-up period – ATP cohort for efficacy

Duration (years) of follow-up period	HRV	Placebo
	N=	N=
Total Mean Minimum Q1 Median Q3 Maximum		

N= Number of subjects included in each group in the considered efficacy period
Total= sum of follow-up period expressed in year for the considered efficacy period
Q1 = 25th percentile
Q3 = 75th percentile
Data Source: Appendix I.Ci

Table E 11 Percentage of subjects reporting any RV GE and efficacy of the vaccine during the follow-up period - ATP cohort for efficacy

	n/N					Vaccine Efficacy			P-Value
				95%CI		95%CI			
Group	N	n	%	LL	UL	%	LL	UL	
HRV Placebo									

N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in the considered efficacy period
%= percentage of subjects reporting at least one severe RV GE episode in the considered efficacy period
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value= two-sided asymptotic score test (significant level of α=0.05)
Data Source= Appendix Table IVA and V.A

Table E 12 Percentage of subjects reporting severe RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine during the follow-up period - ATP cohort for efficacy

Severity using Vesikari scale	Group	N	n	n/N %	95%CI LL	UL	Vaccine Efficacy %	95%CI LL	UL	P-value
≥11	HRV Placebo									
≥12	HRV Placebo									
≥13	HRV Placebo									
≥14	HRV Placebo									
≥15	HRV Placebo									
≥16	HRV Placebo									
≥17	HRV Placebo									
≥18	HRV Placebo									
≥19	HRV Placebo									
≥20	HRV Placebo									

N = number of subjects included in each group

n/% = number/percentage of subjects reporting at least one severe RV GE episode with a score ≥X on the Vesikari scale, in each group

95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval

P-value = two-sided asymptotic score test (significant level of α=0.05)

Data Source= Appendix Table IVA and V.A

Table E 13 Percentage of subjects reporting severe RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine during the follow-up period - ATP cohort for efficacy

Severity using Clark scale	Group	N	n	n/N			Vaccine Efficacy			P-value
				%	95%CI LL	UL	%	95%CI LL	UL	
≥17	HRV									
	Placebo									
≥18	HRV									
	Placebo									
≥19	HRV									
	Placebo									
≥20	HRV									
	Placebo									
≥21	HRV									
	Placebo									
≥22	HRV									
	Placebo									
≥23	HRV									
	Placebo									
≥24	HRV									
	Placebo									

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode caused by the circulating wild-type RV with a score ≥X on the Clark scale, in each group
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided asymptotic score test (significant level of α=0.05)
Data Source= Appendix Table V.A

Figure 3 Efficacy of the vaccine against RV GE with a score ≥ X on the Vesikari scale during the follow up period-ATP cohort for efficacy

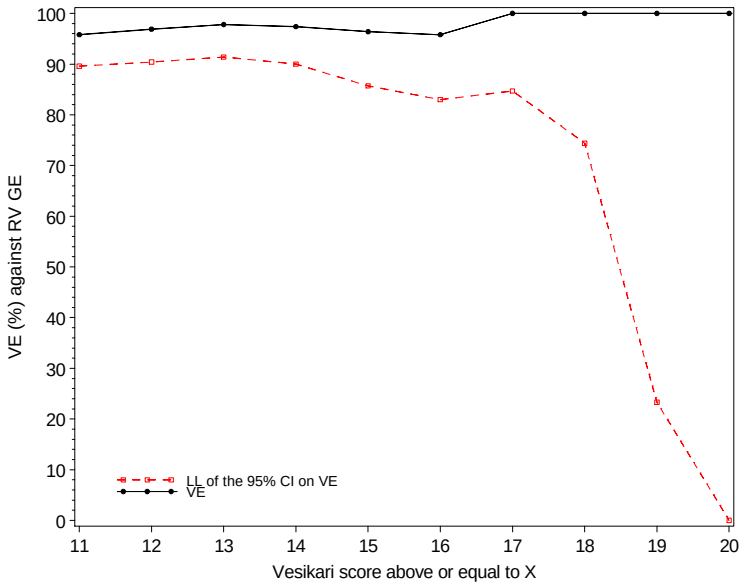


Figure 4 Efficacy of the vaccine against RV GE with a score ≥ X on the Clark scale during the follow up period-ATP cohort for efficacy

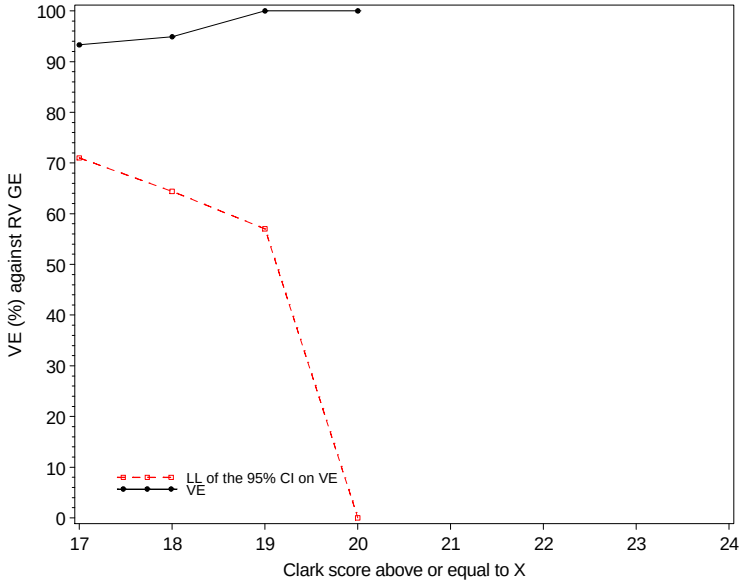


Table E 14 Percentage of subjects reporting severe GE episode (with a score >=11 in using the 20-point Vesikari scale) and efficacy of the vaccine during the follow-up period-ATP cohort for efficacy

Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
HRV									
Placebo									

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized due to RV GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided asymptotic score test (significant level of α=0.05)
Data Source= Appendix Table IVA and V.A

Table E 15 Efficacy of the vaccine against any RV GE during the follow-up period, by Cox – ATP cohort for efficacy

Group	N	n	T (year)	n/T value	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL
HRV									
Placebo									

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized due to RV GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
P-value = two-sided asymptotic score test (significant level of α=0.05)
Data Source= Appendix Table IVA and V.A

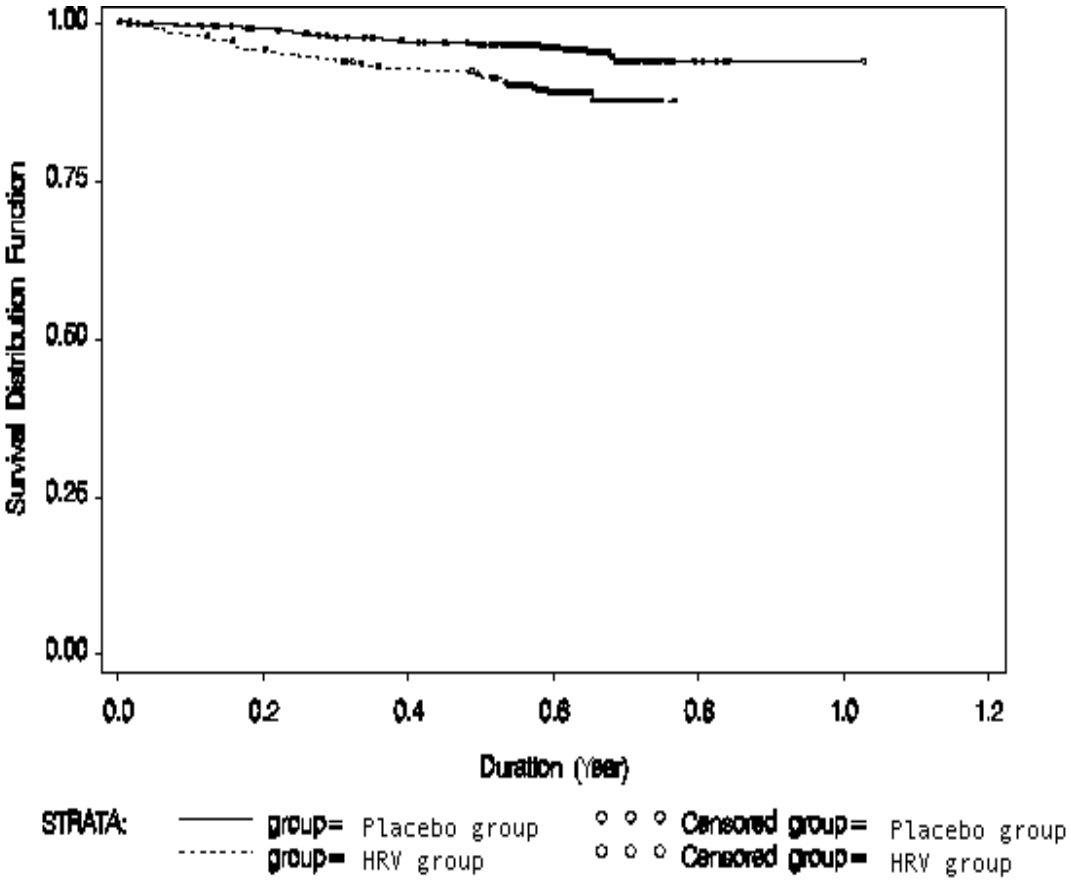
Table E 16 Percentage of subjects who reported GE episodes and RV GE episodes by Year 1 and Year 2- ATP cohort for efficacy

Event		Total number of episodes reported in year 1	HRV		Placebo	
			n	%	n	%
GE	Year 1	1				
		2				
		…				
		Any				
	Year2	1				
		2				
		…				
		Any				
RV GE	Year1	1				
		2				
		…				
		Any				
	Year2	1				
		2				
		…				
		Any				

N = number of subjects included in each group, for the study period
n/% = number/percentage of subjects reporting the specified total number of episode in the considered period
Any = number and percentage of subjects reporting at least one specified episode in the considered period
Data Source = Appendix Table IV.A and V.A

Figure 5 The Kaplan Meier curve for any RV GE / any RV GE due to G1 serotype / any RV GE due to non-G1 serotypes during the follow-up period - ATP cohort for efficacy

(Y-axis can start at 0.50 if not readable):



6. ANNEX 2: CRITERIA FOR ELIMINATING SUBJECTS FROM STAT ANALYSES

Elimination from ATP cohort for efficacy

1040 Administration of concomitant vaccine(s) forbidden in the protocol (**see also eligibility criteria)**

5020 Subjects not entered the surveillance period of the long term follow-up period

Also the elimination codes from secondary year efficacy follow up also applicable.

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.