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.

GlaxoSmithKline Biologicals

Study title

Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.

Study detailed title

A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Clinical Study Report for Study 107625 (Rota-056) (Development Phase III)

Indication Studied: Primary immunisation of healthy infants against rotavirus disease/illness.

Study initiation date:	19 June 2007
Data lock point (Database freeze date):	31 March 2009 (14 July 2009)
Date of report:	25 September 2009
Report Scope:	This report presents the final analyses of all the data up to the data lock point of 31 March 2009. As per the protocol, final analyses was to be done when 28 rotavirus (RV) gastroenteritis (GE) episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest.

Sponsor Signatories: [redacted] M.B.B.S
Director, Rotavirus vaccines
Global Clinical Research and Development
GlaxoSmithKline Biologicals

Dr. [redacted]
Deputy Director, Clinical Development,
GlaxoSmithKline K.K.

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

SYNOPSIS

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 III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Principal investigators: This study was conducted by several principal investigators. Dr. [redacted] was involved in reviewing and approving the study report on behalf of all other investigators.

Study centres: This study was conducted at 20 centres in Japan.

Publication (reference): Not published as of 25 September 2009.

Study period:	**Clinical phase: III**
Study initiation date: 19 June 2007 Data lock point: 31 March 2009	

Objectives:

Primary:

- To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary:

Efficacy

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.
- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

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)

Immunogenicity [in the immunogenicity subset (N = 60)]

- To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

Study design: Randomised, double-blind, placebo-controlled and multi-centre study with 2 parallel groups: Group HRV lyophilised vaccine (also referred to as HRV group) and Group Placebo. Routine childhood vaccinations could be administered as per local practice. Blood samples were to be collected from subjects in the immunogenicity subset (N = 60) at Day 0 (i.e. Visit 1) and one month post Dose 2 (Visit 3). There was active follow-up for the occurrence of gastroenteritis (GE) episodes leading to medical intervention via telephone contact or other means. As per the protocol, final analyses were to be done when 28 rotavirus (RV) GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest. Final analyses up to the data lock point of 31 March 2009 (when the target of at least 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached) are provided in this report. An annex report will be written to present the efficacy and safety data up to two years of age.

Number of subjects	Total	HRV group	Placebo group
Enrolled and Vaccinated	765	508	257
Completed at data lock point (31 March 2009)	735*	490*	245*
According-To-Protocol (ATP) cohort for Efficacy	748	498	250
ATP cohort for safety	764	507	257
ATP cohort for immunogenicity	54	34	20

[redacted] Hence, there are 735 subjects being shown as having completed the study at data lock instead of the actual 737 subjects having completed the study at data lock point.

Diagnosis and criteria for inclusion: Healthy infants, born after a gestation period of 36 – 42 weeks (inclusive), between and including 6 – 14 weeks (42 – 104 days) of age at the time of the first dose of the HRV vaccine/placebo. Written informed consent was obtained from the parent or guardian of each subject before any study-specific procedures were performed.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule /site: Subjects were to receive two oral doses of the lyophilised formulation of the HRV vaccine according to a 0, 1 month schedule.
Vaccine composition /dose /lot number: Each dose of the lyophilised formulation of GSK Biologicals' HRV vaccine contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 HRV strain, 2.25 mg of Dulbecco's Modified Eagle Medium (DMEM), 9 mg of Sucrose, 18 mg of Dextran, 13.5 mg of Sorbitol, 9 mg of amino acids. The liquid diluent contained 60 mg/mL of Calcium carbonate and 0.25% of xanthane in 1.0 mL water for injection. Lot number AROTA031C was used for the HRV vaccine and lot number AD05A167A was used for the diluent.

Reference vaccine /Comparator, dose and mode of administration, lot no.:
Vaccination schedule /site: Lyophilised placebo was reconstituted with the supplied diluent and the resuspended product was administered orally. Subjects in the placebo group were to receive two oral doses of the placebo according to a 0, 1 month schedule.
Vaccine composition /dose /lot number: One dose of GSK Biologicals' lyophilised placebo contained 2.25 mg of DMEM, 9 mg of Sucrose, 18 mg of Dextran, 13.5 mg of Sorbitol, 9 mg of amino acids. Lot number PROTA002A was used for the placebo. The same diluent was used to reconstitute the HRV vaccine and placebo.

Duration of study: The duration of study up to the data lock point was approximately 1.5 years.

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 efficacy:
For each GE episode leading to medical intervention occurring during the study period, a GE diary card was completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE leading to medical intervention was recorded on the same card. Intensity of the GE episodes was scored using the 20-point Vesikari scoring system, with score ≥11 points considered as severe. Available stool samples collected during each GE episode leading to medical intervention from Visit 1 up to the data lock point of 31 March 2009 were tested at GSK Biologicals using Enzyme Linked immunosorbent assay (ELISA) to detect RV. If positive, the sample was tested by polymerase chain reaction (PCR) to determine the G and the P genotypes. If any G1 RV was detected, vaccine virus was differentiated from the wild type strain by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by reverse hybridisation assay or an equivalent approach.

Primary Endpoint:*

- Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary Endpoints:*

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

*All the endpoints specified in this report cover the time period up to the data lock point.

Criteria for evaluation of Reactogenicity and Safety: Recording of solicited AEs (cough/runny nose, diarrhoea, vomiting, fever, irritability and loss of appetite) during the 8-day (Day 0 – Day 7) follow-up period after each dose. Recording of unsolicited AEs occurring during the 31-day (Day 0 – Day 30) follow-up period after each dose. Recording of serious adverse events (SAEs) occurring during the entire study period up to the data lock point (31 March 2009).

Secondary Endpoints:

- 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/Placebo.
- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Criteria for evaluation of Immunogenicity: Measurement of serum anti-rotavirus IgA antibody concentrations in samples collected from the immunogenicity subset at Visit 1 and Visit 3 using ELISA. The assay cut-off was 20 U/mL.

Secondary Endpoints:

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 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)

Statistical methods:

Analysis of demography: The mean, median and standard deviation of height in centimetre (cm), weight in kilogram (kg) at Visit 1 was calculated per group and overall.

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall. The median, mean, range and standard deviation of age in months at data lock point (31 March 2009) or at last contact if the subject was not available at data lock point was also calculated per group and overall. The racial and gender composition per group was also presented.

Analysis of Efficacy: The duration of the efficacy follow-up period was summarised by group. The percentages of subjects with any and severe RV GE (overall and by RV type) leading to medical intervention from 2 weeks after Dose 2 up to the data lock point were calculated with their 95% Confidence Interval (CI) and compared between groups. The vaccine efficacy for each efficacy endpoint was calculated with its 95% CI. The primary objective was reached if the lower limit of the 95% CI on vaccine efficacy (conditional method) for the HRV group against any RV GE requiring medical intervention caused wild-type RV strains during the efficacy follow-up period was > 0%. Additional supportive and exploratory analyses were performed (i.e. efficacy against GE of any aetiology leading to a medical intervention). An exploratory analysis was performed for vaccine efficacy against any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains by Cox method. Planned additional analyses on vaccine efficacy against hospitalisation due to GE of any aetiology and vaccine efficacy during the period starting from 2 weeks post Dose 2 up to Visit 4 were not performed. The analyses will be part of the annex report.

Analysis of Immunogenicity: For each treatment group, at each time point that anti-rotavirus IgA was measured,

- Seroconversion and their exact 95% CI were calculated.
- Geometric Mean Concentrations (GMCs) and their 95% CI were calculated.

The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between HRV vaccine and Placebo groups was computed.

Analysis of Safety: The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period was tabulated by group, for each dose, for overall doses and per subject. The incidence, with exact 95% CI, of each individual solicited AE, was calculated by group, over the solicited follow-up period, after each dose, for all doses and per subject. The same calculations were done for each individual solicited AE rated as grade "3" and for each individual solicited AE related to vaccination. The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. The unsolicited AEs were not tabulated by Preferred Term (PT) to maintain blinding. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0 – Day 30) follow-up period after any doses with its exact 95% CI was tabulated by group, by System Organ Class (SOC). Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination. Serious adverse events reported during the study period (From dose 1 up to data lock point) were described in detail.

Summary:

Demography Results: In the ATP cohort for efficacy, the mean age was 7.7 weeks (range: 6 to 14 weeks) at Dose 1 of HRV vaccine/placebo, 12.7 weeks (range: 10 to 20 weeks) at Dose 2 of HRV vaccine/placebo and 18.5 months (range: 4 to 24 months) at data lock point or at last contact. All the subjects were of Japanese origin; 47.6% of subjects were female and 52.4% of subjects were male.

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)

Efficacy Results: Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) and the total vaccinated cohort. The mean duration of the efficacy follow-up (from 2 weeks post Dose 2 up to the data lock point) in the ATP cohort for efficacy was 1.31 years in both groups.

Primary Endpoint:

- Significantly fewer subjects in the HRV group reported any RV GE leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (1.8% versus 10.0%, p-value <0.001) from 2 weeks post Dose 2 up to the data lock point. Vaccine efficacy against any RV GE leading to medical intervention caused by the circulating wild-type RV was 81.9% [95% CI: 60.0%; 92.6%]. The primary objective of the study was reached.

Secondary Endpoints:

- Significantly fewer number of subjects in the HRV group reported severe RV GE leading to medical intervention caused by circulating wild-type RV compared to the placebo group (0.2% versus 4.4%, p-value <0.001). Vaccine efficacy against severe RV GE leading to medical intervention caused by circulating wild-type RV was 95.4% [95% CI: 68.6%; 99.9%].
- The number of subjects with report of any RV GE leading to medical intervention caused by G1 wild type in the HRV group was lesser compared to the placebo group (0.2% versus 2.4%, p-value 0.014). Vaccine efficacy against any RV GE leading to medical intervention caused by G1 wild-type was 91.6% [95% CI: 31.0%; 99.8%].
- When considering all isolated non-G1 types (G2, G3, G4 and G9), significantly fewer subjects in the HRV group reported any RV GE leading to medical intervention compared with the placebo group (1.6% versus 7.6%, p-value <0.001). Vaccine efficacy against any RV GE leading to medical intervention caused by non-G1 types was 78.9% [95% CI: 49.4%; 92.0%].
- Severe RV GE caused by G1 wild-type leading to medical intervention was reported for 1.6% of the subjects in the placebo group. There were no reports of severe RV GE leading to medical intervention caused by G1 wild-type RV in the HRV group (p-value 0.025). Vaccine efficacy against severe RV GE leading to medical intervention caused by G1 wild-type RV was 100% [95% CI: 24.0%; 100.0%].
- When considering all isolated non-G1 types (G3 and G9), fewer subjects in the HRV group reported severe RV GE leading to medical attention compared to the placebo group (0.2% versus 2.8%, p-value 0.005). Vaccine efficacy against severe RV GE leading to medical intervention caused by non-G1 types was 92.8% [95% CI: 44.2%; 99.8%].
- There were few reports of hospitalisation due to RV GE (1 subject in each group).
- From Dose 1 up to the data lock point: Vaccine efficacy against any RV GE and severe RV GE leading to medical intervention caused by wild-type RV was 82.5% [95% CI: 61.4%; 92.8%] and 95.8% [95% CI: 71.5%: 99.9%], respectively.

Table 1: Vaccine efficacy from 2 weeks post Dose 2 up to the data lock point (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 leading to medical intervention (Primary efficacy endpoint)									
HRV	498	9	1.8	0.8	3.4	81.9	60.0	92.6	<0.001
Placebo	250	25	10.0	6.6	14.4	-	-	-	-

Table continued on the next page

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)

			n/N			Vaccine Efficacy			
				95% CI			95% CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Severe RV GE due to circulating wild-type RV leading to medical intervention*									
HRV	498	1	0.2	0.0	1.1	95.4	68.6	99.9	<0.001
Placebo	250	11	4.4	2.2	7.7	-	-	-	-
Any RV GE due to wild-type G1									
HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
Placebo	250	6	2.4	0.9	5.2	-	-	-	-
Severe RV GE due to wild-type G1*									
HRV	498	0	0.0	0.0	0.7	100.0	24.0	100.0	0.025
Placebo	250	4	1.6	0.4	4.0	-	-	-	-
Any RV GE due to non-G1 types									
HRV	498	8	1.6	0.7	3.1	78.9	49.4	92.0	<0.001
Placebo	250	19	7.6	4.6	11.6	-	-	-	-
Severe RV GE due to non-G1 types*									
HRV	498	1	0.2	0.0	1.1	92.8	44.2	99.8	0.005
Placebo	250	7	2.8	1.1	5.7	-	-	-	-
Hospitalisation due to RV GE									
HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
Placebo	250	1	0.4	0.0	2.2	-	-	-	-

*episodes with score ≥ 11 points on Vesikari scale; N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases; Database lock date = 31MAR2009

Reactogenicity and Safety Results: The reactogenicity and safety analyses were performed on the total vaccinated cohort.

- From Day 0 to Day 7 after any HRV vaccine/placebo doses, the percentage of subjects with reports of any AEs (solicited or unsolicited) including those rated as grade "3" and those assessed as related to vaccination were similar in both groups.
- Irritability was the most frequently reported solicited AE after each dose in both groups (51.4% subjects in the HRV group and 48.6% subjects in the placebo group). Grade "3" solicited AEs were reported in less than 2.0% of the subjects after each dose in both groups.
- The percentage of subjects with report of at least one unsolicited AE classified by MedDRA SOC was 54.9% in the HRV group and 56.0% in the placebo group.
- From Dose 1 up to the data lock point, 13.6% of the subjects in the HRV group and 16.0% of the subjects in the placebo had report of at least one SAE. None of these SAEs were assessed to be causally related to vaccination.
- There were no fatal events reported up to the data lock point.
- There was no significant safety data received after the database freeze date for this study.

Withdrawals due to adverse events /serious adverse events:

- [redacted] This medical condition developed 20 days after receiving Dose 2. The screens for Visit 5 were not yet filled at the time of database freeze hence; further information on this subject is not yet available.

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)

Immunogenicity Results in the immunogenicity subset: Immunogenicity analysis was performed on the ATP cohort for immunogenicity.

- The anti-rotavirus IgA antibody seroconversion rate was 85.3% [95% CI: 68.9%; 95.0%] in the HRV group and 5.0% [95% CI: 0.1%; 24.9%] in the placebo group at one month post Dose 2 of HRV vaccine/placebo.
- Anti-rotavirus IgA antibody GMCs calculated on seropositive subjects were 368.9 U/mL in the HRV group and 496.0 U/mL in the placebo group (only one subject was seropositive at Visit 3 in the placebo group).

Conclusions:

Efficacy

- Two oral doses of GSK Biologicals' HRV vaccine were highly efficacious in preventing any RV GE leading to medical intervention caused by circulating wild-type RV strains during the period starting from 2 weeks post Dose 2 up to the data lock point with a vaccine efficacy of 81.9% [95% CI: 60.0%; 92.6%]. The primary objective of this study was met.
- Two oral doses of the HRV vaccine were efficacious during the period starting from 2 weeks post Dose 2 up to the data lock point in protecting infants against:
  - Severe RV GE leading to medical intervention caused by the circulating wild-type RV with a vaccine efficacy of 95.4% [95% CI: 68.6%; 99.9%].
  - Any RV GE RV leading to medical intervention caused by G1 wild-type with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
  - Severe RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 100% [95% CI: 24.0%; 100.0%].
  - Any RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 78.9% [95% CI: 49.4%; 92.0%].
  - Severe RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 92.8% [95% CI: 44.2%; 99.8%].
- There were few reports of hospitalisation due to RV GE (1 subject in each group).
- During the period starting from Dose 1 up to the data lock point, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 82.5% [95% CI: 61.4%; 92.8%] and 95.8% [95% CI: 71.5%: 99.9%], respectively.

Reactogenicity and Safety

- There was no evidence of a clinically meaningful difference between the HRV group and placebo group for SAEs reported from Dose 1 up to the data lock point or unsolicited AEs reported during the 31-day (Day 0 – Day 30) follow-up period after any dose.
- The reactogenicity profile of two doses of HRV vaccine was similar to that of the placebo in terms of the solicited AEs reported during the 8-day (Day 0 – Day 7) follow-up period after each dose.

Immunogenicity

- Two doses of the HRV vaccine were immunogenic as shown by the anti-rotavirus IgA antibody seroconversion rate of 85.3% [95% CI: 68.9%; 95.0%] in the HRV group at one month post Dose 2 of the HRV vaccine.

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
$CCID_{50}$	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	Combined diphtheria, tetanus- acellular cell pertussis
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
GE	Gastroenteritis
GMC	Geometric mean concentration
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IRB	Institutional Review Board
IS	Intussusception
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
PCR	Polymerase Chain Reaction
PMDA	Pharmaceutical and Medical Devices Agency
PT	Preferred Term
RDE	Remote Data Entry

RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SBIR	Internet Randomisation tool
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 was 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 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.
Completed:	Subjects who were available at the data lock point (31 March 2009).
Diary card:	Cards given to the parents /guardians by the investigator to record adverse events following vaccination.
Efficacy follow-up period for the ATP analysis:	Period starting from two weeks after Dose 2 of HRV vaccine or placebo up to the data lock point of 31 March 2009 when 28 RV GE cases leading to medical intervention and caused by the circulating wild-type RV strains was accumulated.
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.
Gastroenteritis:	Diarrhoea with or without vomiting.
Medical intervention:	Defined as medical doctor visit, an emergency room visit or hospitalisation.
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.
RV GE for primary efficacy analysis:	An episode of any severity GE leading to a medical intervention occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (mL) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.
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).
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subject(s):	Term used throughout the protocol to denote an individual whose parent/guardian was contacted in order to 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 parents /guardians.

Treatment number:	A unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.
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 was 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, amendments, the informed consent, and other information that required pre-approval were reviewed and approved by each investigational centre IRB.

1.2. Ethical conduct of the study

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

1.3. Subject information and consent

Written informed consent was obtained from each parent /guardian prior to the performance of any study-specific procedures. Electronic case report forms were used for each subject's data to be recorded.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

This study was conducted at 20 centres in Japan by several principal investigators. Dr. [redacted] was involved in reviewing and approving the study report on behalf of the other investigators.

GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium was the study sponsor and was responsible for administrative aspects 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 HRV vaccine clinical development. In this capacity, the IDMC periodically reviewed all Serious Adverse Events (SAEs) reported during this study till 31 December 2007. IDMC was dissolved on 18 February 2008.

3. INTRODUCTION

Rotaviruses (RVs) are the leading cause of severe gastroenteritis (GE) among young children aged <5 years. A recent review estimated that RV is accountable for more than 527000 (475 000 – 580 000) deaths per year [WHO, 2007]. Although the majority of these deaths occur in developing countries, the disease is not limited to poor settings. In

developed countries, RV infection rarely results in death but RV remains the most common cause of hospitalisation for GE in children and leads to major medical and societal costs [Glass, 1996]. In a hospital based study in Japan, RV was detected in approximately 58% of children aged less than 5 years who were hospitalised for acute GE indicating that RV was the most important pathogen causing hospitalisation among infants and young children in Japan [Nakagomi, 2005].

RV diarrhoea represents an important global public health problem, and the development of a vaccine has been given a high priority by the World Health Organisation (WHO). A prophylactic approach is particularly important for this disease, as the incidence of RV diarrhoea does not differ importantly between developing and developed countries, and, thus, it is unlikely that sanitary or general hygiene improvements will have a great impact on its incidence [Perez-Vargas, 2006].

To meet this health need, GlaxoSmithKline (GSK) Biologicals has developed an attenuated vaccine which is based on a human rotavirus (HRV) strain designated as RIX4414. The vaccine strain RIX4414 was derived from the parent 89-12 HRV strain belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old child with a mild RV diarrhoea in December 1988. A candidate vaccine based on the 89-12 HRV strain at passage 33 in African Green Monkey Kidney cells was shown to be safe, immunogenic and efficacious against RV GE over two consecutive RV seasons in infants [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002]. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilised HRV vaccine containing RIX4414, a cloned passage 43 derivative from 89-12, for oral administration after reconstitution with a separately supplied liquid calcium carbonate buffer.

GSK Biologicals' HRV vaccine has been extensively tested in clinical studies conducted in infants from Europe, North America, Latin America and the Caribbean, Asia and Africa. The overall safety profile of the HRV vaccine was similar to the placebo. A large phase III study in 63,225 infants demonstrated that the HRV vaccine is not associated with an increased risk of intussusception (IS) during 31-day period after vaccination with either of the two doses of HRV vaccine when compared to placebo [Ruiz Palacios, 2006]. In post-marketing experience, cases of IS have been reported in temporal association with the HRV vaccine. Most of the cases were reported within 7 days following the first dose. However, no causal relationship has been established. In clinical studies, two doses of HRV vaccine were well tolerated, immunogenic and highly effective against RV GE hospitalisations, severe RV GE and any RV GE due to multiple circulating RV strains (G1 and non-G1 RV types) [Vesikari, 2004; Salinas, 2005; Ruiz Palacios, 2006]. Efficacy results from Latin America demonstrate the HRV vaccine is highly efficacious, providing 85% protection against severe RV GE episodes, which reaches 100% for the most severe dehydrating episodes [Vesikari, 2006]. In another phase III study performed in Europe, efficacy was of 87% (80%-92%) against any RV GE and of 96% (90%-99%) against severe RV GE [Vesikari, 2006].

This study was undertaken to provide the Regulatory Authorities in Japan with immunogenicity, efficacy, safety and reactogenicity data for GSK Biologicals' HRV vaccine when used in Japanese infants aged approximately 2 months at the time of the

first dose. The study is currently ongoing and the efficacy follow-up will be up to the time that the infants are approximately two years of age. As per the protocol, final analyses were to be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest. This study report contains final analysis of efficacy, reactogenicity, safety and immunogenicity data of all subjects up to the data lock point of 31 March 2009 (when the target of at least 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached). Results of the analysis for the efficacy and safety data collected at Visit 5 (approximately 2 years of age) will be provided in an annex report.

4. STUDY OBJECTIVES

4.1. Primary objective

- To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

See Section 5.11.1 for the primary endpoint.

4.2. Secondary objectives

Efficacy

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.
- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity [in the immunogenicity subset (N = 60)]

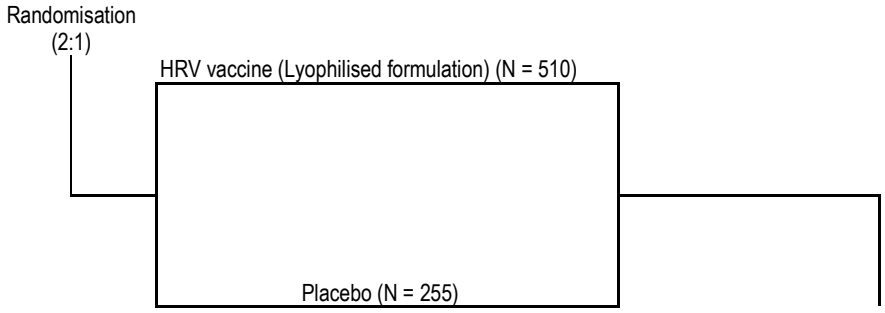
- To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

See Section 5.11.2 for the secondary endpoints.

5. INVESTIGATIONAL PLAN

5.1. Study design

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



	Vaccination Visits			Safety and efficacy follow-up Visits	
	Visit 1	Visit 2	Visit 3	Visit 4#	Visit 5#
	Dose 1	Dose 2			
	Day 0	Month 1	Month 2		
Age:	6 – 14 weeks			1 year	2 years
	Blood sampling*		Blood sampling*		

N: Number of subjects planned to be enrolled.
HRV: Human rotavirus
*: Blood sampling in the immunogenicity subset (N = 60)
#: Safety and efficacy follow-up visits.

5.1.1. Overall study design – Description

- Experimental design: Phase III, randomised, double-blind, placebo-controlled, multicenter study in Japan with two parallel groups.
- Treatment allocation: Randomised (2:1 ratio).
- Blinding: Double-blind. Blinding will be maintained till the end of the study, i.e. Visit 5.
- Treatment Groups:
  - Group HRV lyophilised vaccine (also referred to as HRV group) (N = 510)
  - Group Placebo (N = 255)
- Vaccination schedule: Vaccination according to 0, 1 month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks (42–104 days) at the time of the first dose.
- Control: Placebo.
- Routine childhood vaccination according to local practice could be administered concurrently with the study vaccinations as recommended in Japan. All vaccines administered from birth up to Visit 3 were to be documented in the electronic case report form (eCRF).
- Eight day (Day 0 – Day 7) follow-up period for solicited AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) after each dose of HRV vaccine/Placebo using diary cards. Unsolicited AEs were to be followed up for a period of 31 days (Day 0 – Day 30) after each dose.
- During the entire study period (from Dose 1 up to Visit 5 [two years of age]), active follow-up for occurrence of GE episodes (diarrhoea) leading to medical intervention via telephone contact or other means (at least every two weeks).
- For each GE episode leading to medical intervention occurring during the study period,
  - a GE diary card was to be completed daily until end of the GE symptoms.
  - a stool sample was to be collected as soon as possible after symptoms began but preferably not later than 7 days after the onset of GE symptoms.
- Recording of SAEs throughout the study period.
- Blood samples (1 ml of whole blood to provide 0.4 mL of serum) were to be collected from subjects in the immunogenicity subset (N = 60) at Day 0 (i.e. Visit 1) and one month post Dose 2 (Month 2 i.e. Visit 3) to measure anti-rotavirus IgA antibody concentrations.
- Type of study: Self-contained.
- Data collection: Remote Data Entry (RDE).
- Five scheduled visits per subject: at Months 0, 1, 2 and one and two years of age.

- Duration of the study: The duration of the study up to the data lock point was approximately 1.5 years.
- As per the protocol, final analyses were to be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest.

  Final analyses up to the data lock point of 31 March 2009 are provided in this report. An annex report will be written to present the efficacy and safety data up to two years of age.

5.2. Study procedures

5.2.1. Outline of study procedures

Table 1 presents the outline of study procedures.

Table 1 List of study procedures

Age	6-14 weeks			One year	Two years
Visits Timing Sampling time point	VISIT 1 Day 0 Pre-vacc	VISIT 2 Month 1	VISIT 3 Month 2 Post-vacc 2	VISIT 4	VISIT 5
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	●	●	-	-	-
Randomisation	●	-	-	-	-
Blood sampling (1 ml) for antibody determination in an immunogenicity subset *	●	-	●	-	-
Study vaccination (HRV vaccine/ Placebo)	●	●	-	-	-
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians	●	●	-	-	-
Return of reactogenicity diary card	-	○	○	-	-
Transcription of the reactogenicity diary card		●	●	-	-
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●	-	-
Record any concomitant medication/vaccination, by investigator	●	●	●	●#	●#
Recording of GE leading to medical intervention occurring throughout the study period	●	●	●	●	●
Contact the subject's parent/guardian to check GE occurrence at least every two weeks	○	○	○	○	○
Collection of stool samples if subject has GE leading to medical intervention	●	●	●	●	●
Return of GE diary card	-	○	○	○	○
GE diary card transcription	-	●	●	●	●
Recording of SAEs	●	●	●	●	●
Reporting AEs leading to drop-out	●	●	●	●	●
Conclusion at Visit 4				●	
Study conclusion	-	-	-	-	●

Note: Final analyses were to be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest.
As the study is still ongoing, some subjects are yet to complete Visit 5.
● was used to indicate a study procedure that required documentation in the individual eCRF.
○ was used to indicate a study procedure that does not require documentation in the individual eCRF.
Blood sampling was done only from subjects in the immunogenicity subset (N = 60).
for concomitant medication administered for the treatment of an AE leading to drop-out/SAE.

5.2.2. Intervals between study visits

The intervals between study visits are presented in Table 2.

Table 2 Intervals between study visits

Interval /Visit	Range of interval /Visit	Length of Adapted Interval
Visit 1→Visit 2	30 – 48 days	21 – 48 days
Visit 2→Visit 3	30 – 48 days	21 – 48 days
Visit 4	1 year of age ± 15 days	-
Visit 5	2 years of age ± 15 days	-

N.B: The reference date for intervals between study visits: the first vaccination date.

5.3. Selection of study population

Target enrolment was 765 subjects (510 subjects in HRV lyophilised vaccine group and 255 subjects in the placebo group). All subjects were enrolled at multiple sites in Japan.

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) were to be enrolled in the study.
- A male or female infant 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/guardian of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born between a gestation period of 36 and 42 weeks inclusive.

5.3.2. Exclusion criteria

The following criteria were to be 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 within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- History of use of experimental rotavirus vaccine.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs prior to the first vaccine dose. (For corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids were allowed.)
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition determined by the investigator.

- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).
- A family history of congenital or hereditary immunodeficiency.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.
- 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. Axillary temperature <37.5°C.) Temperature greater than or equal to these cut-offs warrants deferral of the vaccination pending recovery of the subject.
- Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of RV GE.
- Concurrently participating in another clinical study, at any time during the study period in which the subject had been or would have been exposed to an investigational or a non-investigational product (pharmaceutical product or device).

5.3.3. Elimination criteria

The following criteria were to be 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 determined a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 5.11.4 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids were allowed).
- Administration of immunoglobulin 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

The following adverse events (AEs) constituted absolute contraindications to further administration of HRV vaccine/Placebo; if any of these AEs occurred during the study, the subject did 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.

- Known hypersensitivity after previous administration of HRV vaccine or to any component of the vaccine.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

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

- Acute severe febrile illness.
- Diarrhoea or vomiting.

5.3.5. Subject completion and withdrawal at the time of data lock point

5.3.5.1. Subject availability at the time of data lock point

A subject who was available at the time of the data lock point was considered to have completed this case triggered analysis.

5.3.5.2. Subject Withdrawal

Subjects who were withdrawn because of AEs were clearly distinguished from subjects who were withdrawn for other reasons. Investigators followed subjects who were withdrawn as result of a SAE/AE until resolution of the event.

Withdrawals were not replaced.

5.3.5.3. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study will be any subject who does not come back for the concluding visit (Visit 5)/was not available for the concluding contact foreseen in the protocol. A 'withdrawal' from this current study was any subject who was not available at the time of data lock point.

A subject qualified as a 'withdrawal' from the study when no study procedure had occurred, no follow-up had been performed and no further information had been collected for this subject from the date of withdrawal/last contact.

Investigators made an attempt to contact those subjects who did not return for scheduled visits or follow-up.

Information relative to the withdrawal was to be documented on the Study Conclusion page of the eCRF. The investigator was to 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 (was to be specified)
- consent withdrawal, not due to an adverse event
- moved from the study area
- lost to follow-up
- other (was to be specified).

5.3.5.4. Subject withdrawal from administration of the investigational product

A 'withdrawal' from the investigational product was any subject who did not receive the complete treatment, i.e. when no further planned dose was 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 have been performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational product was to be documented on the Vaccine Administration page of the eCRF. The investigator was to 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 (was to be specified).

5.4. Composition and administration of vaccines

The lyophilised formulations of HRV vaccine/Placebo used in this study have been developed and manufactured by GSK Biologicals. The Quality Control Standards and Requirements for the candidate vaccine were described in separate release protocols and the required approvals were obtained.

Commercial vaccines (including GSK vaccines) were assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

5.4.1. Description of vaccines

Table 3 gives the detailed formulation of the HRV vaccine/Placebo.

Table 3 Composition of the GSK Biologicals' HRV lyophilised vaccine and Placebo

Vaccine	Formulation	Presentation	Volume	Lot Number
LYOPHILISED FORMULATION				
GSK Biologicals' HRV lyophilised vaccine	RIX4414 HRV strain at least $10^{6.0}$ $CCID_{50}$ Dulbecco's Modified Eagle Medium (DMEM) 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised vaccine in a monodose glass vial Diluent (calcium carbonate buffer) supplied separately.	Not applicable	AROTA031C
GSK Biologicals' Placebo for HRV lyophilised vaccine	DMEM 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised Placebo in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable	PROTA002A
GSK Biologicals. calcium carbonate buffer	Calcium carbonate 60 mg/mL Xanthane 0.25% in 1.0 ml water for injection	Liquid buffer in prefilled syringe	at least 1.1 ml	AD05A167A

5.4.2. Dosage and administration

5.4.2.1. Lyophilised formulation of HRV vaccine/Placebo

To prepare GSK Biologicals' HRV lyophilised vaccine/placebo for administration, the entire content of the supplied diluents (calcium carbonate buffer) was transferred from the oral applicator into the vial of the lyophilised product (HRV vaccine/placebo) via the intermediate device. The vial was shaken well to resuspend the vaccine. The entire volume of the resuspended product (approximately 1 mL) was withdrawn into the same oral applicator and 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 was administered. The subject could continue to participate in the study.

The vaccinees were 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.

The vaccination regimen is summarised in Table 4.

Table 4 Dosage and Administration

Visit	Vaccination	Dose	Vaccine	Route
1, 2	Rotavirus/Placebo	1	Lyophilised HRV vaccine/ Placebo	Oral

5.4.3. Treatment allocation and randomisation

Target enrolment was 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the Placebo Group) to obtain 612 evaluable subjects (408 subjects in the HRV group and 204 subjects in the Placebo Group) for the evaluation of the primary objective.

The actual treatment number used for first vaccination of the subject was to be recorded by the investigator in the eCRF (Randomisation/Treatment Allocation Section).

5.4.3.1. Randomisation of supplies

A randomisation list was generated at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program and was used to number the vaccines. A randomisation blocking scheme (2:1 ratio) was used to ensure that balance between treatments was maintained: a single treatment number identified uniquely the vaccine doses 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, 5% over-randomisation of supplies was prepared.

The vaccine doses were distributed to each study centre, respecting the randomisation block size.

5.4.3.2. Randomisation of subjects

The treatment allocation at the investigator site was performed using a central randomisation system on Internet (SBIR). The randomisation algorithm used a minimisation procedure accounting for centre.

After having checked that a subject was eligible, the person in charge of the vaccination accessed the randomisation system on Internet. Upon providing a subject number for the subject, the randomisation system used the minimisation algorithm to determine the treatment number to be used for the subject.

If the internet was unavailable, the subjects were administered the vaccine number with the highest number still available at the vaccination site.

5.4.3.3. Subset for immunogenicity

A subset of 60 subjects was to be part of the immunogenicity subset. Due to foreseeable difficulty in obtaining consent for withdrawal of blood from subjects, only those subjects whose parents/guardians consented were enrolled in this immunogenicity subset. This subset was centre specific and not all the centres enrolled subjects in to this subset. All subjects in this subset were to provide blood samples to explore immunogenicity of the HRV vaccine/Placebo.

5.4.4. Blinding

The study is being conducted in a double-blind manner with respect to HRV vaccine and placebo. The parents/guardians of the subjects, the study personnel and the investigator are unaware of the study vaccine administered (HRV vaccine or placebo). Blinding will be maintained for the whole study period. Since the final analysis was done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period, access to the individual treatment decode during the final analysis was limited to an external statistician and the database administrator to maintain double blinding until study end. This allowed unbiased evaluation of the study vaccine.

The investigator, or person designated by the investigator, contacted GSK Biologicals' Central Safety physician directly or via the local safety contact to discuss the need for emergency unblinding. The GSK Biologicals' Central Safety Office accessed the individual randomisation code. The code was broken by the GSK Biologicals' Central Safety physician only in the case of medical events that the investigator/physician in charge of the subject felt cannot be treated without knowing the identity of the study vaccine.

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) was to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which was unexpected and attributable/suspected, prior to regulatory reporting. The Clinical Safety physician was responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs.

5.5. 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 31 days after each dose of study vaccine 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 or at any time during the study period up to Visit 3 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.

Any vaccine not foreseen in the study protocol administered since birth up to Visit 3 is to be recorded with trade name, route of administration and date(s) of administration.

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 [Axillary temperature <37.5°C (99.5°F)] 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 leading to drop-out 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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

5.6. Laboratory assays and time points

Table 5 presents the laboratory assays with their cut-off.

Table 5 Laboratory Assays

Antibody	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Core Laboratory
Rotavirus IgA	ELISA	In-house	U/mL	20	GSK Biologicals, Rixensart*

ELISA: Enzyme-linked immunosorbent assay
U/mL: units/millilitre
* GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals

Table 6 presents the immunological read-outs for the study.

Table 6 Immunological read-outs

Sampling time point			Marker	Planned number of subjects
Timing	Month	Visit number		
Serology (in a subset of subjects [N = 60])				
Pre	Day 0	1	HRV IgA	60
Post-vacc 2	Month 2	3	HRV IgA	60
GE stool analysis				
From Visit 1 to Visit 5			RV antigen	All

5.7. Assessment of efficacy variables

Active follow-up for occurrence of GE leading to medical intervention was conducted during the period starting from administration of Dose 1 up to the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or Placebo until end of study visit, the intention was to make contact with each subject's parent/guardian at least once every two weeks to check on the occurrence of any GE leading to medical intervention. This contact was by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or health care workers or other convenient means. All contacts were logged. In case of unavailability of subject's parent/guardian at the time of contact, at least one more attempt was made before the next planned contact.

For each GE episode leading to medical intervention occurring during the study period, a GE diary card was completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE leading to medical intervention was recorded on the same card. The completed diary cards were returned to the investigator at the following study visit.

Data Collection for GE cases

Any GE episode (defined as diarrhoea with or without vomiting) leading to a medical intervention starting from Visit 1 to study end was to be documented using the GE diary card. The following information was to be collected on the GE diary card during each GE episode: Axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given.

Medical attention (medical doctor visit, emergency room visit or hospitalisation) was also recorded for each GE episode.

Vesikari scale to assess intensity of GE episodes

The information collected on the GE diary card allowed the assessment of the intensity of each GE episode using a 20-point scoring system.

In the 20-point scoring system, points were assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy or hospitalisation for each episode of GE as shown in Table 7.

Table 7 The 20-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	2
≥ 6	3
Maximum number of looser than normal stools /24 hours	
1-3	1
4-5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2-4	2
≥ 5	3
Fever*	
Axillary	
36.6 – 37.9°C	1
38.0 – 38.4°C	2
≥ 38.5°C	3
Dehydration	
1-5%	2
≥ 6%	3
Treatment	
Rehydration	1
Hospitalisation	2

* The highest temperature recorded during the episode was scored.

A score < 7 was prospectively defined as mild, a score 7 - 10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe.

Periodic contact was made with the subjects' family to enquire about the occurrence of GE leading to a medical intervention. Collection of a stool sample was requested if not yet provided and if GE occurred since last contact. For a GE considered to be an SAE, the SAE screen/form in the eCRF was completed.

Collection of stool samples during GE

Parents/guardians were instructed to collect stool sample(s) from the subject if the subject developed GE leading to medical intervention during the entire study period. A stool sample was to be collected as soon as possible after illness began and preferably not later than 7 days after the start of the GE episode. A stool sample was to be collected for each GE episode. A second stool sample was to be collected if the first sample was insufficient. Two occurrences of GE were classified as separate episodes, if there were 5 or more diarrhoea-free days between the episodes.

Analysis of stool samples during GE

Available stool samples collected during each GE episode leading to medical intervention from Visit 1 up to the data lock point of 31 March 2009 were tested at GSK Biologicals using Enzyme Linked immunosorbent assay (ELISA) to detect RV. If positive, the sample was tested by polymerase chain reaction (PCR) to determine the G and the P genotypes. If any G1 RV was detected, vaccine virus was differentiated from the wild type serotype by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) followed by reverse hybridisation assay or an equivalent approach.

5.7.1. Immunological correlates of protection

No immunological correlate of protection has been demonstrated so far for the HRV antigen used in the HRV vaccine.

5.8. Assessment of immunogenicity variables

Serum obtained from whole blood samples collected from subjects in the immunogenicity subset at Visit 1 and Visit 3 were tested by ELISA at GSK Biologicals' central laboratory to measure serum anti-rotavirus IgA antibody concentrations. The assay cut-off was 20 U/mL.

5.9. Assessment of safety variables

5.9.1. Adverse events

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.

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 was evaluated by the investigator. As a consistent method of soliciting AEs, the subject's parent/guardian was 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. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination were established.

Investigators followed-up subjects:

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

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

When an AE/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 an AE/SAE 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. vital signs) 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 5.9.1 or SAE, as defined in Section 5.9.2. 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that were present or detected at the start of the study and did not worsen, were not 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.

Assessment of Intensity

The intensity of the solicited AEs were assessed as described in Table 8.

Table 8 Intensity scales used by the parents/guardians for solicited symptoms

Adverse Event	Intensity grade	Parameter
Fever*		Record temperature in °C using an axillary thermometer
Fussiness/Irritability	0 1 2 3	Behaviour as usual Crying more than usual/no effect on normal activity Crying more than usual/interfered with normal activity Crying that could not be comforted/prevents normal activity
Diarrhoea¶		Recorded the number of looser than normal stools/day
Vomiting§		Recorded the number of vomiting episodes/day
Loss of appetite	0 1 2 3	Normal Ate less than usual/no effect on normal activity Ate less than usual/interferes with normal activity Not eating at all
Cough/runny nose	0 1 2 3	Normal Cough/runny nose which was easily tolerated Cough/runny nose which interfered with daily activity Cough/runny nose which prevented daily activity

*Fever was defined as temperature ≥ 37.5°C as measured by an axillary thermometer.
¶Diarrhoea 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 maximum intensity of diarrhoea, fever and vomiting occurring during the solicited 8-day (Day 0 – Day 7) follow-up period were scored at GSK Biologicals as described in Table 9.

Table 9 Intensity scales used at GSK Biologicals' for diarrhoea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	Intensity grade	Parameter
Diarrhoea	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	Temperature axillary < 37.5°C
	1	Temperature axillary ≥ 37.5 – ≤ 38.0°C
	2	Temperature axillary > 38.0 – ≤ 39.0°C
	3	Temperature axillary > 39.0°C

The intensity of each AE and SAE recorded in the eCRF or SAE Report Form, as applicable, was assigned to one of the following categories:

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 school/kindergarten/a day-care centre and caused the parents/guardians to seek medical advice.)

An AE that was assessed as grade 3 (severe) was not necessarily the same as a SAE. Grade 3 was a category utilised for rating the intensity of an event; and both AEs and SAEs could be assessed as grade 3. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in Section 5.9.2.

Assessment of causality

The investigator was obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator used 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 was considered and investigated. The investigator

also consulted the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

In case of concomitant administration of multiple vaccines, it may not have been possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator, therefore should have assessed whether the AE was causally related to vaccination rather than to the individual vaccines.

Causality of all other AEs was assessed by the investigator using the following question:

"Was there a reasonable possibility that the AE (or SAE) may have been caused by the investigational product?"

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

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined "serious", it was examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine, if applicable
- Erroneous administration
- Other cause (was to be specified).

Assessment of Outcome

Outcome of any non-serious AE or any SAE reported during the entire study were assessed as:

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

5.9.2. Serious adverse events

A serious adverse event (SAE) was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' referred to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe.

c. required hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation signified that the subject was 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 occurred during hospitalisation were AEs. If a complication prolonged hospitalisation or fulfilled any other serious criteria, the event was serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE was considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE.

d. resulted in disability/incapacity, or

NOTE: The term disability meant a substantial disruption of a person's ability to conduct normal life functions. This definition was 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 have interfered or prevented everyday life functions but did not constitute a substantial disruption.

e. 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 that may not have been immediately life-threatening or resulted in death or hospitalisation but may have jeopardised the subject or may have required 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 did not result in hospitalisation.

The standard time period for collecting and recording SAEs began at randomisation or the first receipt of the HRV vaccine/Placebo and will end at the last study visit (i.e. Visit 5) following administration of the last dose of the HRV vaccine/Placebo for each subject.

The investigator inquired about the occurrence of AEs/SAEs at every visit/contact during the study and throughout the follow-up phase as appropriate.

GSK Biologicals may have requested the investigator to 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 was then obliged to assist. If a subject died during participation in the study or during a recognised follow-up period, GSK Biologicals was to be provided with a copy of any available post-mortem findings, including histopathology.

5.10. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, case report form and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the company representative(s) prior to study start. Investigator meetings were held prior to the study start in each centre.

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).

Independent Audit statement:

- This study was subject to audit by GlaxoSmithKline's department of Worldwide Regulatory Compliance-GCP (WRC-GCP).
- This study was subject to audit by GlaxoSmithKline's Regulatory Compliance in Japan.

5.11. Statistical methods

All statistical analyses were performed using SAS 9.1 and Proc StatXact-7.

Final analysis was done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period. This final analysis was run by an independent analysis centre in order to preserve blinding as much as possible. However, due to regulatory requirements associated with the clinical report, fatalities and drop-out were planed to be unblinded. In addition, planned summaries may have led to inadvertent unblinding.

This report presents data up to the data lock point (31 March 2009). An annex report will present the efficacy/safety data up to two years of age.

5.11.1. Primary endpoint

- Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

5.11.2. Secondary endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- 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/Placebo.
- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Immunogenicity (in the immunogenicity subset N = 60)

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 3.

5.11.3. Determination of sample size

The primary objective was to determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine could prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Target enrolment was 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the Placebo Group) to obtain 612 evaluable subjects (408 subjects in the HRV lyophilised vaccine group and 204 subjects in the Placebo Group) with an attrition rate of 20% of non-evaluable subjects for the evaluation of the primary objective.

Considering a 2:1 randomisation ratio and various incidence rates, Table 10 provides the power that the 95% confidence interval (CI) for vaccine efficacy (VE) will be above 0% and 10%.

Therefore, for an 8% attack rate of RV GE leading to a medical intervention in the placebo group from 2 weeks after Dose 2 up to 2 years of age, and if the vaccine efficacy was truly 80%, the study has 92% power to observe a 95% CI for the vaccine efficacy that would be above 10%. It was expected to observe a total of 28 RV GE leading to a medical intervention during the efficacy follow-up period in the total vaccinated cohort.

In Japan, medical intervention risk due to RV GE is reported in 50% of children until 6 years of age which is not the school age. Supposing that the 50% risk is observed every year, it can be calculated that the attack rate of the annual RV GE is 8.3% (50/6). The RV GE cases reported in 2005/2006 season seems to be low compared with those in past years. We have estimated that the attack rate of RV GE during the 2 years is 8% considering yearly fluctuation of the attack rate.

Table 10 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 612 evaluable subjects - 408 subjects in HRV group and 204 subject in the Placebo Group, power based on 1.000 simulations using Proc StatXact)

Incidence rate in the Placebo for any RV GE leading to a medical intervention	VE (%)	Power to have a lower limit of the 95%CI on VE ≥ 0%	Power to have a lower limit of the 95%CI on VE ≥ 10%
10%	80%	97%	96%
	70%	90%	83%
8%*	80%**	94%	92%
	70%	82%	74%
7%	80%	90%	86%
	70%	75%	67%
5%	80%	76%	69%
	70%	59%	50%

* anticipated rate in the Placebo for any RV GE leading to a medical intervention
**anticipated vaccine efficacy

5.11.4. Study cohorts /data sets analysed

5.11.4.1. Total Vaccinated cohort

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

- a safety analysis based on the total vaccinated cohort included all vaccinated subjects,
- an immunogenicity analysis based on the total vaccinated cohort included all vaccinated subjects from the immunogenicity subset for whom immunogenicity data was available.

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

5.11.4.2. ATP cohort for efficacy

The ATP cohort for efficacy included all subjects:

- who received two doses of HRV vaccine or placebo,
- who entered the efficacy surveillance period:
  - had follow-up beyond 2 weeks after Dose 2 of study vaccination,
- who had no rotavirus other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks after Dose 2 of HRV vaccine or placebo,
- for whom the randomisation code was not broken,
- who did not receive a vaccine forbidden by or not specified in the protocol.

5.11.4.3. ATP cohort for safety

The ATP cohort for safety included all vaccinated subjects:

- who received at least one dose of HRV vaccine or placebo,
- for whom the randomisation code was not broken,
- who did not receive a vaccine forbidden by or not specified in the protocol.

5.11.4.4. ATP immunogenicity cohort

The ATP immunogenicity cohort included all subjects from the ATP safety cohort:

- who did not receive 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,
- for whom immunogenicity data was available, at pre and post sampling time points.
- who had no rotavirus other than vaccine strain in GE stool samples collected up to Visit 3.
- who had no concomitant infection unrelated to the vaccine which may have influenced the immune response.
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1.

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

The total vaccinated cohort was used for the analysis of safety.

The ATP cohort for immunogenicity was used for the analysis of immunogenicity.

5.11.5. Derived and transformed data

Demography

For a given subject and a given demographic variable, missing measurements were 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.

Safety

Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) were treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan was re-assessed to ensure more accurate reporting of study data by further analysis.

Immunogenicity

The cut-off value of anti-rotavirus IgA antibody was defined by the laboratory before the analysis and is described in Section 5.6.

- A seronegative subject was a subject whose concentration was below the cut-off value.
- A seropositive subject was a subject whose concentration was greater than or equal to the cut-off value.
- Seroconversion was defined as the appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (mL) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.

The geometric mean concentration (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.

5.11.6. Analysis of demographics

The mean, median and standard deviation of height in centimetre (cm), weight in kilogram (kg) at Visit 1 was calculated per group and overall.

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall. The median, mean, range and standard deviation of age in months at data lock point (31 March 2009) or at last contact if the subject was not available at data lock point was also calculated per group and overall. The racial and gender composition per group was also presented.

The distribution of subjects enrolled among the study centres was tabulated as a whole and per group.

Summary of feeding practice on the day of each study vaccination was tabulated by group and overall.

5.11.7. Analysis of Efficacy

Vaccine efficacy was calculated, with their 95% CI against:

- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to G1 serotype caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to non-G1 serotypes during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to data lock point.

The primary objective was reached if the lower limit of the 95% CI on vaccine efficacy (conditional method) for the HRV group against any RV GE requiring medical intervention caused wild-type RV strains during the efficacy follow-up period was > 0%.

Additional supportive and exploratory analyses were performed (i.e. efficacy against GE of any aetiology leading to a medical intervention). An exploratory analysis was performed for vaccine efficacy against any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains by Cox method.

Vaccine efficacy, derived from a Cox regression model on the time to first event with censoring at the data lock or subjects without event. The model includes the group as fixed effect [Kalbfleisch, 2002].

Incidence rate in a group (P) was computed as the number of subjects reporting at least one event (n)/total follow-up time to a first event censored at the data lock date (T). The associated 95% CI's was obtained considering that n follows a Poisson distribution with P*T parameter.

The number of events prevented by 100 vaccinated infant-years was obtained from 100 times the difference in the incidence rate. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].

5.11.8. Analysis of Safety

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period was tabulated by group, for each dose, for overall doses and per subject.

The incidence, with exact 95% CI, of each individual solicited AE, was calculated by group, over the solicited follow-up period, after each dose, for all doses and per subject. The same calculations were done for each individual solicited AE rated as grade "3" and for each individual solicited AE related to vaccination.

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. The unsolicited AEs were not tabulated by Preferred Term (PT) to maintain blinding. The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0 – Day 30) follow-up period after any doses with its exact 95% CI was tabulated by group, by System Organ Class (SOC). Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

Serious adverse events reported during the study period (From dose 1 up to data lock point) were described in detail. The SAEs were not tabulated by PT to maintain blinding.

5.11.9. Analysis of Immunogenicity

In a subset of subjects

For each treatment group, at each time point that anti-rotavirus IgA was measured,

- Seroconversion and their exact 95% CI were calculated.
- GMCs and their 95% CI were calculated.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 was displayed using reverse cumulative curves (RCCs).

The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between HRV vaccine and Placebo groups was computed.

5.11.10. Interim analysis

There was no interim analysis planned for this study.

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

5.12.1. Protocol amendment

Amendment 1: The protocol was amended on 07 May 2007 to implement changes requested by the Pharmaceutical and Medical Devices Agency (PMDA) in Japan.

5.12.2. Other changes

The following were the changes from the protocol:

- The final analysis (case triggered analysis) was run by an independent analysis centre in order to preserve blinding as much as possible. However, due to regulatory requirements associated to the clinical report, fatalities and dropouts were planned to be unblinded.
- An exploratory analysis was performed for vaccine efficacy against severe RV GE by Cox method.
- A summary table on co-administered, concomitant vaccinations and concomitant medications received during the study period was generated.
- Planned additional analyses on the vaccine efficacy against hospitalisation due to GE of any aetiology and vaccine efficacy during the period starting from 2 weeks post Dose 2 up to Visit 4 were not performed. The analyses will be part of the annex report.

The following are the changes from the reporting and analysis plan (RAP):

- The dropouts at the first year conclusion were summarised.
- The characteristics of any RV GE episodes were computed for the efficacy follow-up period on ATP cohort for efficacy.
- A column for “Total” was added to feeding practices tables.
- The overall analysis on feeding practices was also performed.

All other analyses were performed as planned in the protocol and RAP.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject came for the first study visit on 19 June 2007 and the data lock point for the study is 31 March 2009.

6.2. Subject eligibility and attrition from the study

6.2.1. Number of subjects

Table 11 presents the number of subjects by centre for the total vaccinated cohort.

A total of 765 subjects were enrolled and received at least one dose of the HRV vaccine or placebo.

Table 11 Number of subjects by centre (Total vaccinated cohort)

	HRV	Placebo	Total	
Center	n	n	n	%
[redacted]	26	14	40	5.2
	28	14	42	5.5
	18	8	26	3.4
	26	13	39	5.1
	18	10	28	3.7
	12	7	19	2.5
	13	7	20	2.6
	38	19	57	7.5
	13	7	20	2.6
	68	34	102	13.3
	32	16	48	6.3
	14	7	21	2.7
	16	8	24	3.1
	6	4	10	1.3
	48	24	72	9.4
	48	24	72	9.4
	72	35	107	14.0
	3	2	5	0.7
	3	2	5	0.7
	6	2	8	1.0
All	508	257	765	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 = GSK Biologicals' assigned centre number

Supplement 1 presents the minimum and maximum activity dates.

6.2.2. Study completion and withdrawal from study

Note: As the study is still ongoing, this study report contains all the data that was available at the time of the data lock point.

Table 12 presents the number of subjects vaccinated, completed and withdrawn from the study at the data lock point with reasons for withdrawn.

Supplement 2 presents the number of subjects vaccinated, completed and withdrawn from the study at Visit 4 with reasons for withdrawal.

Of the 765 subjects who received at least one dose of the HRV vaccine or placebo, a total of 737 subjects (490 subjects in the HRV group, 245 subjects in the placebo group and an additional 2 subjects) completed the study and 28 subjects were withdrawn from the study at data lock point. [redacted]

- The parent/guardian of one subject in the placebo group withdrew their child from the study due to a non-serious AE (Anaphylaxis). This subject experienced the AE 38 days after receiving Dose 2 of placebo. The AE lasted only for a day and the subject was withdrawn from the study after Visit 3.
- One subject in the placebo group was withdrawn from the study by the investigator due to a protocol violation. This subject received a dose Bacille Calmette-Guérin (BCG) vaccine 15 days after receiving Dose 1 of placebo.
- The parents/guardians of 12 subjects (9 subjects in the HRV group and 3 subjects in the placebo group) withdrew consent for their children to participate in the study. Consent withdrawal for these subjects was not due to an AE.
- A total of 11 subjects (8 subjects in the HRV group and 3 subjects in the placebo group) migrated from the study area and hence were unable to complete the study.
- Three subjects in the placebo group with complete vaccination course were lost to follow-up.

Table 12 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at data lock (Total vaccinated cohort)

	HRV	Placebo	Total
Number of subjects vaccinated	508	257	765
Number of subjects completed at database lock (31-MAR-2009)	490*	245*	735*
Number of subjects withdrawn	17	11	28
Reasons for withdrawal :			
Serious Adverse Event	0	0	0
Non-serious adverse event	0	1	1
Protocol violation	0	1	1
Consent withdrawal (not due to an adverse event)	9	3	12
Migrated/moved from study area	8	3	11
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	3	3
Others	0	0	0

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed at database lock point
Withdrawn = number of subjects who withdrew before database lock point

[redacted] Hence, there are 735 subjects being shown as having completed the study at database lock instead of the actual 737 subjects having completed the study at database lock point.

6.2.3. Protocol deviations

The number of subjects enrolled and included in the ATP cohort for efficacy along with reasons for subjects excluded from the ATP cohort for efficacy is summarised in Table 13.

Total Vaccinated Cohort

A total of 765 subjects were enrolled into the study. All subjects (508 subjects in the HRV group and 257 subjects in the placebo group) were part of the total vaccinated cohort with at least one dose of the HRV vaccine or placebo administered.

ATP Cohort for Efficacy

Of the 765 subjects included in the total vaccinated cohort, 17 subjects were eliminated from the ATP cohort for efficacy for the following reasons:

- The randomisation code was broken for one subject in the HRV group (elimination code 1060). Refer to Section 8.4 for details.
- A total of 16 subjects (9 subjects in the HRV group and 7 subjects in the placebo group) were eliminated with code 3010 because of incomplete vaccination schedule.

Thus, a total of 748 subjects (498 subjects in the HRV group and 250 subjects in the placebo group) were included in the ATP cohort for efficacy.

Table 13 Number of subjects enrolled into the study as well as the number excluded from ATP cohort for efficacy with reasons for exclusion

	Total			HRV		Placebo	
Title	n	s	%	n	s	n	s
Total cohort	765						
Total vaccinated cohort	765		100	508		257	
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0
At least one study vaccine dose not administered. (code 3010)	16	16		9	9	7	7
ATP cohort for efficacy	748		97.8	498		250	

Note: Subjects may 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 vaccinated cohort

Table 14 presents the number of subjects enrolled and included in the ATP analyses (safety, reactogenicity and immunogenicity) along with the reasons for exclusion. Subjects could be attributed more than one elimination code.

ATP cohort for safety

Of the 765 subjects included in the total vaccinated cohort, 1 subject in the HRV group was eliminated from the ATP cohort for safety because the randomisation code was broken (elimination code 1060). Refer to 8.4 for details.

Thus, a total of 764 subjects (507 subjects in the HRV group and 257 subjects in the placebo group) were included in the ATP cohort for safety.

ATP cohort for immunogenicity

Of the 764 subjects included in the ATP cohort for safety, 710 subjects were excluded from the ATP cohort for immunogenicity for the following reasons:

- Three subjects in the HRV group were eliminated with code 2100 because blood samples were not collected for 2 subjects while the blood sampling result was invalid for one subject.
- A total of 707 subjects (470 subjects in the HRV group and 237 subjects in the placebo group) were eliminated with code 2130 because these subjects were not part of the immunogenicity subset and hence blood samples were not planned to be drawn from them.

Thus, a total of 54 subjects (34 subjects in the HRV group and 20 subjects in placebo group) were included in the ATP cohort for immunogenicity.

Table 14 Number of subjects enrolled into the study as well as the number excluded from ATP analyses (Reactogenicity/Safety and Immunogenicity) with reasons for exclusion

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	765						
Total vaccinated cohort	765		100	508		257	
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0
ATP cohort for safety	764		99.9	507		257	
Essential serological data missing (code 2100)	3	3		3	3	0	0
Subject not planned to be bled for their all blood sampling visits (code 2130)	707	708		470	471	237	237
ATP cohort for immunogenicity	54		7.1	34		20	

Note: Subjects may 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 vaccinated cohort

The number of subjects with deviations from specifications for age mentioned in the study inclusion criteria and intervals between study visits are presented in Supplement 3 and Supplement 4.

6.3. Demographic characteristics

6.3.1. ATP cohort for efficacy

Table 15 presents the summary of demographic characteristics for the ATP cohort for efficacy.

A summary of feeding practices at Dose 1 and Dose 2 of HRV vaccine or placebo for the ATP cohort for efficacy is presented in Supplement 5.

- The mean age was 7.7 weeks (range: 6 to 14 weeks) at Dose 1 of HRV vaccine/placebo, 12.7 weeks (range: 10 to 20 weeks) at Dose 2 of HRV vaccine/placebo and 18.5 months (range: 4 to 24 months) at data lock point or at last contact. All the subjects were of Japanese origin; 47.6% of subjects were female and 52.4% of subjects were male.
- The percentage of subjects who were breast-fed at the time of both doses of HRV vaccine or placebo was 58.2% (Supplement 5).

Table 15 Summary of demographic characteristics (ATP cohort for efficacy)

		HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at dose 1 of HRV/placebo	Mean	7.7	-	7.7	-	7.7	-
	SD	1.96	-	2.06	-	2.00	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	6	-	6	-
	Maximum	14	-	14	-	14	-
Age (weeks) at dose 2 of HRV/placebo	Mean	12.7	-	12.7	-	12.7	-
	SD	2.03	-	2.18	-	2.08	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	19	-	20	-	20	-
Age (months) at database lock(31MAR2009)/ at the last contact	Mean	18.5	-	18.4	-	18.5	-
	SD	2.21	-	2.56	-	2.33	-
	Median	19.0	-	19.0	-	19.0	-
	Minimum	4	-	4	-	4	-
	Maximum	24	-	23	-	24	-
Gender	Female	225	45.2	131	52.4	356	47.6
	Male	273	54.8	119	47.6	392	52.4
Race	African heritage / African American	0	-	0	-	0	-
	American Indian or Alaskan native	0	-	0	-	0	-
	Asian - Central/South Asian heritage	0	-	0	-	0	-
	Asian - East Asian heritage	0	-	0	-	0	-
	Asian - Japanese heritage	498	100	250	100	748	100
	Asian - South east Asian heritage	0	-	0	-	0	-
	Native Hawaiian or other Pacific Islande	0	-	0	-	0	-
	White - Arabic / North African heritage	0	-	0	-	0	-
	White - Caucasian / European heritage	0	-	0	-	0	-
	Other	0	-	0	-	0	-
Height (cm) at Visit 1	Mean	56.5	-	56.5	-	56.5	-
	SD	2.76	-	2.76	-	2.76	-
	Median	56.0	-	56.0	-	56.0	-
Weight (kg) at Visit 1	Mean	5.2	-	5.1	-	5.2	-
	SD	0.76	-	0.71	-	0.74	-
	Median	5.1	-	5.0	-	5.1	-

N = total number of subjects in each group
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
Database Lock Date = 31MAR2009

6.3.2. Total vaccinated cohort

Supplement 6 presents the summary of demographic characteristics of the total vaccinated cohort.

A summary of feeding practices at Dose 1 and Dose 2 of HRV vaccine or placebo for the total vaccinated cohort is presented in Supplement 7.

- The mean age was 7.7 weeks (range: 5 to 14 weeks) at Dose 1 of HRV vaccine/placebo, 12.7 weeks (range: 10 to 20 weeks) at Dose 2 of HRV vaccine/placebo and 18.3 months (range: 1 to 24 months) at data lock point or at last contact.
- The percentage of subjects who were breast-fed at the time of both doses of HRV vaccine or placebo was 58.2%.
- One subject was unblinded before the data lock point (31 March 2009) (Supplement 8). Refer to Section 8.4 for details.

6.3.3. ATP cohort for immunogenicity

Supplement 9 presents the summary of demographic characteristics for the ATP cohort for immunogenicity.

The mean age was 7.4 weeks (range: 6 to 12 weeks) at Dose 1 of HRV vaccine/placebo, 12.4 weeks (range: 10 to 17 weeks) at Dose 2 of HRV vaccine/placebo and 19.5 months (range: 12 to 22 months) at data lock point or at last contact.

6.4. Concomitant and Intercurrent Vaccinations

Routine childhood vaccinations according to local practice could be administered concurrently with the study vaccinations as recommended in Japan.

Supplement 10 presents the summary of co-administered vaccinations by dose for the total vaccinated cohort.

- The percentage of subjects who received concomitant vaccinations with Dose 1 and Dose 2 of HRV vaccine/placebo was not more than 4.3%. Diphtheria and tetanus toxoids and acellular pertussis (DTPa) and Hepatitis B virus (HBV) vaccines were co-administered with HRV vaccine/placebo.

A summary of vaccinations other than HRV vaccine or placebo administered during the study period excluding vaccinations given on the same day of HRV vaccine or placebo doses is presented in Supplement 11.

- BCG, DTPa, HBV and Oral Poliovirus vaccine (OPV) were administered between study visits. The percentage of subjects who received vaccinations other than HRV vaccine or placebo between study visits was 0.5% (prior to Dose 1), 3.5% (between Dose 1 and Dose 2) and 40.7% (between Dose 2 and Visit 3).

7. VACCINE EFFICACY RESULTS

7.1. Data sets analysed

Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) for vaccine efficacy during the period starting from 2 weeks post Dose 2 up to the data lock point and on the total vaccinated cohort for the vaccine efficacy from Dose 1 up to the data lock point. See Section 5.11.4 for the definition of the cohorts identified for analyses and Section 6.2 for eligibility for analyses.

Table 16 presents a summary of GE episodes leading to medical intervention with vaccine strain isolated.

Vaccine virus was not isolated from any of the GE stool samples collected in the study from Dose 1 up to data lock point.

Table 16 Percentage of subjects with vaccine virus in gastroenteritis stool samples collected in case of a GE episode leading to medical intervention from Dose 1 up to database lock - Total vaccinated cohort

				95% CI	
Group	**N**	**n**	**%**	**LL**	**UL**
HRV	508	0	0.0	0.0	0.7
Placebo	257	0	0.0	0.0	1.4

N= Number of subjects in each group
n (%) = Number (percentage) of subjects with vaccine virus in at least one sample collected in case of GE episode
95% CI = Exact 95% confidence interval: LL = Lower limit: UL = upper limit
Database Lock date = 31 MAR 2009

7.2. ATP cohort for efficacy

The ATP cohort for efficacy included 748 subjects (498 subjects in the HRV group and 250 subjects in the placebo group).

7.2.1. Characterisation of GE episodes leading to medical intervention

Table 17 presents the percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to the data lock point. Table 18 presents the summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to the data lock point.

- A total of 191 subjects (38.4%) from the HRV group and 100 subjects (40.0%) from the placebo group had report of at least one GE episode leading to medical intervention.
- Of all the GE episodes leading to medical intervention that were tested, rotavirus was detected in 9 GE episodes (1.8%) in the HRV group and 25 GE episodes (10.0%) in the placebo group.

- When the GE and RV GE episodes leading to medical intervention were scored using the 20-point Vesikari scale, the distribution of reported GE episodes leading to medical intervention among mild, moderate and severe intensity was similar in both groups but there were more cases rated as severe (≥11 points) in terms of RV GE episodes in the placebo group (11 RV GE episodes [44.0%]) as compared to the HRV group (1 RV GE episode [11.1%]) (Table 18).

Table 17 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes, and severe RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

		HRV N = 498		Placebo N = 250		Total N = 748	
Event	Total number of episodes reported	n	%	n	%	n	%
GE	1	130	26.1	65	26.0	195	26.1
	2	39	7.8	22	8.8	61	8.2
	3	12	2.4	11	4.4	23	3.1
	4	8	1.6	1	0.4	9	1.2
	6	0	0.0	1	0.4	1	0.1
	7	2	0.4	0	0.0	2	0.3
	Any	191	38.4	100	40.0	291	38.9
RV GE	1	9	1.8	25	10.0	34	4.5
	Any	9	1.8	25	10.0	34	4.5
Severe GE	1	41	8.2	26	10.4	67	9.0
	2	1	0.2	5	2.0	6	0.8
	3	1	0.2	0	0.0	1	0.1
	5	1	0.2	0	0.0	1	0.1
	Any	44	8.8	31	12.4	75	10.0
Severe RV GE	1	1	0.2	11	4.4	12	1.6
	Any	1	0.2	11	4.4	12	1.6

N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified total number of episode
Any = number (percentage) of subjects reporting at least one specified symptom = sum of the "Total number of episodes reported"
Database Lock date = 31MAR2009

Table 18 Number of GE episodes and RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to database lock by severity using the 20 point Vesikari scale - ATP cohort for efficacy

		HRV		Placebo	
Event	**Severity using the 20 point Vesikari scale**	**n**	**%**	**n**	**%**
GE	**Mild (1-6)**	119	41.0	60	39.5
	Moderate (7-10)	120	41.4	56	36.8
	Severe (≥11)	51	17.6	36	23.7
	Any	290	100	152	100
RV GE	**Mild (1-6)**	6	66.7	6	24.0
	Moderate (7-10)	2	22.2	8	32.0
	Severe (≥11)	1	11.1	11	44.0
	Any	9	100	25	100

n (%) = number (percentage) of specified events reported in each group, by severity using the 20 point Vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy follow-up period
Database Lock date = 31MAR2009

Supplement 12 and Supplement 13 present the percentage of subjects with RV GE episodes and severe RV GE episodes by G and P genotype, respectively.

Table 19 presents the number of severe RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to the data lock point, by G and P genotype.

Among the severe RV GE episodes leading to medical intervention, G3P[8] (5 episodes in the placebo group) was the most predominant RV type circulating during the efficacy period. The other RV types isolated were G1P[8] wild type (4 episodes in the placebo group) and G9P[8] (1 episode in the HRV group and 2 episodes in the placebo group).

Table 19 Number of severe RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to database lock , by G and P type - ATP cohort for efficacy

Serotype	**HRV N'= 1**		**Placebo N'= 11**	
	n	**%**	**n**	**%**
G1WT+P8WT	0	0.00	4	36.36
G3+P8WT	0	0.00	5	45.45
G9+P8WT	1	100.0	2	18.18

N'=number of severe RV GE episodes reported in the considered efficacy period
n (%) = number (percentage) of sever RV GE episodes reported in the considered efficacy period, by serotype
Database lock date = 31MAR2009

Supplement 14 presents the number of RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to the data lock point, by G and P genotype.

Among the RV GE episodes leading to medical intervention, G3P[8] (3 episodes in the HRV group and 12 episodes in the placebo group) was the most predominant RV type circulating during the efficacy period. The other RV types isolated were G9P[8] (3

episodes in the HRV group and 5 episodes in the placebo group), G1P[8] wild type (1 episode in the HRV group and 6 episodes in the placebo group), G2P[4] (1 episode each in both groups) and G4P[8] (1 episode each in both groups).

Supplement 15 presents the characteristics of severe RV GE episodes leading to medical intervention based on the Vesikari scale reported from 2 weeks post Dose 2 up to the data lock point.

Supplement 16 presents the characteristics of severe RV GE episodes leading to medical intervention based on the Vesikari score by G9 type reported from 2 weeks post Dose 2 up to the data lock point.

Supplement 17 characteristics of any RV GE episodes leading to medical intervention based on the Vesikari scale reported from 2 weeks post Dose 2 up to the data lock point.

Supplement 18 to Supplement 22 present the characteristics of RV GE episodes leading to medical intervention based on Vesikari score by G types reported from 2 weeks Dose 2 up to the data lock point.

Supplement 23 presents the distribution of the Vesikari score for RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to the data lock point.

The incidence of RV GE leading to medical intervention rated 6 and below on the Vesikari scale was similar in both groups but the incidence of RV GE leading to medical intervention rated more than 6 on the Vesikari scale was much higher in the placebo group as compared to the HRV group.

Supplement 24 presents the duration (in years) of efficacy follow-up from 2 weeks post Dose 2 up to the data lock point.

The mean duration of the efficacy follow-up period from 2 weeks post Dose 2 up to the data lock point was 1.31 years in the HRV group and placebo group.

7.2.2. Vaccine efficacy against any RV GE leading to medical intervention (primary endpoint)

Table 20 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild-type RV leading to medical intervention from 2 weeks post Dose 2 up to the data lock point.

- Significantly fewer subjects in the HRV group reported any RV GE leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (1.8% versus 10.0%, p-value <0.001) from 2 weeks post Dose 2 up to the data lock point. Vaccine efficacy against any RV GE leading to medical intervention caused by the circulating wild-type RV was 81.9% [95% CI: 60.0%; 92.6%]. The primary objective of the study was reached since the lower limit of the 95% CI on vaccine efficacy was >0% (criteria specified for fulfilling the primary efficacy objective).

Table 20 Percentage of subjects reporting any RV GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks after dose 2 to data lock - ATP cohort for efficacy

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	9	1.8	0.8	3.4	81.9	60.0	92.6	<0.001
Placebo	250	25	10.0	6.6	14.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

Using the Cox proportional-hazard model, vaccine efficacy against any RV GE leading to medical intervention caused by the circulating wild-type RV was 82.7% [95 CI: 62.94%; 91.92%]. A total of 6.6 any RV GE episodes leading to medical intervention per 100 infant year could be prevented by vaccination (Supplement 25 and Supplement 27).

7.2.3. Vaccine efficacy against severe RV GE leading to medical intervention

Table 21 presents the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV from 2 weeks post Dose 2 up to the data lock point.

- Significantly fewer subjects in the HRV group reported severe RV GE leading to medical intervention caused by circulating wild-type RV compared to the placebo group (0.2% versus 4.4%, p-value <0.001). Vaccine efficacy against severe RV GE leading to medical intervention caused by circulating wild-type RV was 95.4% [95% CI: 68.6%; 99.9%].

Table 21 Percentage of subjects reporting severe RV GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 to database lock - ATP cohort for efficacy

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	1	0.2	0.0	1.1	95.4	68.6	99.9	<0.001
Placebo	250	11	4.4	2.2	7.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

Using the Cox proportional-hazard model, vaccine efficacy against severe RV GE leading to medical intervention caused by the circulating wild-type RV was 95.5% [95% CI: 65.40%; 99.42%]. A total of 3.2 severe RV GE episodes leading to medical

intervention per 100 infant year could be prevented by vaccination (Supplement 26 and Supplement 27).

7.2.4. Vaccine efficacy against circulating RV types

7.2.4.1. Vaccine efficacy against any RV GE leading to medical intervention by RV type

Table 22 presents the efficacy of the HRV vaccine against any RV GE leading to medical intervention, by isolated RV types from 2 weeks post Dose 2 up to the data lock point.

- The number of subjects with report of any RV GE leading to medical intervention caused by G1 wild type in the HRV group was lesser compared to the placebo group (0.2% versus 2.4%, p-value 0.014). Vaccine efficacy against any RV GE caused by G1 wild-type leading to medical intervention was 91.6% [95% CI: 31.0%; 99.8%].
- When considering all isolated non-G1 types (G2, G3, G4 and G9), significantly fewer subjects in the HRV group reported any RV GE leading to medical intervention compared with the placebo group (1.6% versus 7.6%, p-value <0.001). Vaccine efficacy against any RV GE caused by non-G1 types leading to medical intervention was 78.9% [95% CI: 49.4%; 92.0%].
- Any RV GE episodes caused by G2 and G4 types were reported for 0.2% of subjects in the HRV group and 0.4% of subjects in the placebo group (p-value 1.000). Vaccine efficacy against any RV GE caused by G2 and G4 types was 49.8% [95% CI: -3840.6%; 99.4%].
- Significantly fewer subjects in the HRV group reported any RV GE episodes caused by G3 type compared with the placebo group (0.6% versus 4.8%, p-value <0.001). Vaccine efficacy against any RV GE caused by G3 type was 87.4% [95% CI: 53.5%; 97.7%].
- Any RV GE episodes caused by G9 type were reported for 0.6% of subjects in the HRV group and 2.0% of subjects in the placebo group (p-value 0.178). Vaccine efficacy against any RV GE caused by G9 type was 69.9% [95% CI: -54.8%; 95.3%].
- Any RV GE episodes caused by P[4] type was reported for 0.2% of subjects in the HRV group and 0.4% of subjects in the placebo group (p-value 1.000). Vaccine efficacy against any RV GE caused by P[4] type was 49.8% [95% CI: -3840.6%; 99.4%].
- Significantly fewer subjects in the HRV group reported any RV GE episodes caused by P[8] type compared with the placebo group (1.6% versus 9.6%, p-value <0.001). Vaccine efficacy against any RV GE caused by P[8] type was 83.3% [95% CI: 61.5%; 93.5%].

Table 22 Percentage of subjects reporting any RV GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock, by RV types - ATP cohort for efficacy

				n/N			VE			
Serotype	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
	Placebo	250	6	2.4	0.9	5.2	-	-	-	-
G2	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
G3	HRV	498	3	0.6	0.1	1.8	87.4	53.5	97.7	<0.001
	Placebo	250	12	4.8	2.5	8.2	-	-	-	-
G4	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
G9	HRV	498	3	0.6	0.1	1.8	69.9	-54.8	95.3	0.178
	Placebo	250	5	2.0	0.7	4.6	-	-	-	-
P4	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
P8	HRV	498	8	1.6	0.7	3.1	83.3	61.5	93.5	<0.001
	Placebo	250	24	9.6	6.2	13.9	-	-	-	-
Pooled Non-G1	HRV	498	8	1.6	0.7	3.1	78.9	49.4	92.0	<0.001
	Placebo	250	19	7.6	4.6	11.6	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Database lock date = 31MAR2009

7.2.4.2. Vaccine efficacy against severe RV GE leading to medical intervention by RV type

Table 23 presents the efficacy of the HRV vaccine against severe RV GE leading to medical intervention, by isolated RV types from 2 weeks post Dose 2 up to the data lock point.

- Severe RV GE caused by G1 wild-type leading to medical intervention was reported for 1.6% of the subjects in the placebo group. There were no reports of severe RV GE caused by G1 wild-type RV leading to medical intervention in the HRV group. Vaccine efficacy against severe RV GE caused by G1 wild-type RV leading to medical intervention was 100% [95% CI: 24.0%; 100.0%].
- When considering all isolated non-G1 types (G3 and G9), fewer subjects in the HRV group reported severe RV GE leading to medical attention compared to the placebo group (0.2% versus 2.8%, p-value 0.005). Vaccine efficacy against severe RV GE caused by non-G1 types was 92.8% [95% CI: 44.2%; 99.8%].
- Severe RV GE caused by G3 type was reported for 2.0% of the subjects in the placebo group. There were no reports of severe RV GE caused by G3 type RV leading to medical intervention in the HRV group. Vaccine efficacy against severe RV GE caused by G3 type RV leading to medical intervention was 100% [95% CI: 45.2%; 100.0%].

- Severe RV GE episodes caused by G9 type were reported for 0.2% of subjects in the HRV group and 0.8% of subjects in the placebo group (p-value 0.521). Vaccine efficacy against severe RV GE caused by G9 type was 74.9% [95% CI: -382.2%; 99.6%].
- Significantly fewer subjects in the HRV group reported severe RV GE episodes caused by P[8] type compared with the placebo group (0.2% versus 4.4%, p-value <0.001). Vaccine efficacy against severe RV GE caused by P[8] type was 95.4% [95% CI: 68.6%; 99.9%].

Table 23 Percentage of subjects reporting severe RV GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks after Dose 2 up to database, by RV types - ATP cohort for efficacy

				n/N			VE			
Serotype	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV	498	0	0.0	0.0	0.7	100.0	24.0	100.0	0.025
	Placebo	250	4	1.6	0.4	4.0	-	-	-	-
G3	HRV	498	0	0.0	0.0	0.7	100.0	45.2	100.0	0.008
	Placebo	250	5	2.0	0.7	4.6	-	-	-	-
G9	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
P8	HRV	498	1	0.2	0.0	1.1	95.4	68.6	99.9	<0.001
	Placebo	250	11	4.4	2.2	7.7	-	-	-	-
Pooled	HRV	498	1	0.2	0.0	1.1	92.8	44.2	99.8	0.005
Non-G1	Placebo	250	7	2.8	1.1	5.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

7.2.5. Vaccine efficacy against hospitalisation due to RV GE

Table 24 presents the efficacy of the HRV vaccine against hospitalisation due to RV GE leading to medical intervention from 2 weeks post Dose 2 up to the data lock point.

- There were few reports of hospitalisation due to RV GE (1 subject in each group).

Table 24 Percentage of subjects hospitalised due to RV GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks after dose 2 up to database lock - ATP cohort for efficacy

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
Placebo	250	1	0.4	0.0	2.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Database lock date = 31MAR2009

7.2.6. Vaccine efficacy against any GE leading to medical intervention

Supplement 28 presents the exploratory analysis performed for efficacy of the HRV vaccine against any GE leading to medical intervention from the period starting from 2 weeks post Dose 2 up to the data lock point.

- Any GE leading to medical intervention was reported for 191 subjects (38.4%) in the HRV group and 100 subjects (40.0%) in the placebo group (p-value 0.776). Vaccine efficacy against any GE leading to medical intervention was 4.1% [95% CI: -23.4%; 25.1%].

7.3. Total Vaccinated Cohort analysis

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

7.3.1. Vaccine efficacy against RV GE leading to medical intervention during the period from Dose 1 up to the data lock point

Supplement 29 to Supplement 40 present the results for vaccine efficacy during the period starting from Dose 1 up to the data lock point.

Efficacy estimates for the period from Dose 1 up to the data lock point (mean duration: 1.45 years in each group) were consistent with the results of the primary analysis on the ATP cohort for efficacy for the period starting from Dose 1 up to the data lock point.

- During the period from Dose 1 up to the data lock point, significantly fewer subjects reported any RV GE caused by wild-type RV leading to medical intervention in the HRV group compared to the placebo group (1.8% versus 10.1%, p-value <0.001). Vaccine efficacy against any RV GE caused by wild-type RV leading to medical intervention was 82.5% [95% CI: 61.4%; 92.8%].
- During the period from Dose 1 up to the data lock point, significantly fewer subjects reported severe RV GE caused by wild-type RV leading to medical intervention in the HRV group compared to the placebo group (0.2% versus 4.7%, p-value <0.001). Vaccine efficacy against severe RV GE caused by wild-type RV leading to medical intervention was 95.8% [95% CI: 71.5%: 99.9%].

7.4. Efficacy Conclusions

- Two oral doses of GSK Biologicals' HRV vaccine were highly efficacious in preventing any RV GE leading to medical intervention caused by circulating wild-type RV strains during the period starting from 2 weeks post Dose 2 up to the data lock point with a vaccine efficacy of 81.9% [95% CI: 60.0%; 92.6%]. The primary objective of this study was met.
- Two oral doses of the HRV vaccine were efficacious during the period starting from 2 weeks post Dose 2 up to the data lock point in protecting infants against:

- Severe RV GE leading to medical intervention caused by the circulating wild-type RV with a vaccine efficacy of 95.4% [95% CI: 68.6%; 99.9%].
- Any RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
- Severe RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 100% [95% CI: 24.0%; 100.0%].
- Any RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 78.9% [95% CI: 49.4%; 92.0%].
- Severe RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 92.8% [95% CI: 44.2%; 99.8%].

- There were few reports of hospitalisation due to RV GE (1 subject in each group).
- During the period starting from Dose 1 up to the data lock point, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 82.5% [95% CI: 61.4%; 92.8%] and 95.8% [95% CI: 71.5%: 99.9%], respectively.

8. SAFETY RESULTS

8.1. Data sets analysed

The analysis of safety was performed on the total vaccinated cohort.

8.2. Total vaccinated cohort analysis

Table 25 presents the number and percentage of subjects who received HRV vaccine or placebo doses.

Majority (at least 97.3%) of the subjects in the HRV group and placebo group received both doses.

Table 25 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort)

	HRV N = 508		Placebo N = 257		Total N = 765	
Total number of doses received	**n**	**%**	**n**	**%**	**n**	**%**
1	9	1.8	7	2.7	16	2.1
2	499	98.2	250	97.3	749	97.9
Any	508	100	257	100	765	100

N = number of subjects in each group or in total included in the considered cohort
n (%) = number (percentage) of subjects receiving the specified total number of doses
Any = number and percentage of subjects receiving at least one dose

The number of doses administered and the number of completed symptom sheets (see definition in glossary of terms) are presented in Supplement 41. Symptom sheets were completed for all doses in both groups, indicating high compliance for reactogenicity reporting.

8.2.1. Overall incidence of adverse events

Table 26 presents the percentage of doses and of subjects with any AE (solicited or unsolicited) reported during the 8 day (Day 0 – Day 7) follow-up period.

Supplement 42 presents the percentage of doses and of subjects reporting grade "3" AEs (solicited or unsolicited) during the 8-day (Day 0 – Day 7) follow-up period.

Supplement 43 presents the percentage of doses and of subjects reporting AEs (solicited or unsolicited) assessed as related to vaccination during the 8-day (Day 0 – Day 7) follow-up period.

- The percentage of subjects with report of any AEs (solicited or unsolicited) during the 8-day (Day 0 – Day 7) follow-up period was similar in both groups (75.8% in the HRV group and 73.5% in the placebo group). There was no increase in the incidence of AEs (solicited or unsolicited) from Dose 1 to Dose 2 of the HRV vaccine.
- The incidence of AEs (solicited or unsolicited) rated as grade "3" in intensity and those assessed as related to vaccination were also similar in both groups (Supplement 42 and Supplement 43).

Table 26 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)

		Any symptoms				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV	508	304	59.8	55.4	64.1
	Placebo	257	142	55.3	48.9	61.4
Dose 2	HRV	499	273	54.7	50.2	59.1
	Placebo	250	127	50.8	44.4	57.2
Overall/dose	HRV	1007	577	57.3	54.2	60.4
	Placebo	507	269	53.1	48.6	57.5
Overall/subject	HRV	508	385	75.8	71.8	79.5
	Placebo	257	189	73.5	67.7	78.8

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n (%)= number (percentage) of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

8.2.2. Solicited general adverse events

Table 27 presents the percentage of subjects reporting each solicited AE including those graded "3" in intensity and those assessed as related to vaccination during the 8-day (Day 0 – Day 7) follow-up period for each dose.

Supplement 44 presents the percentage of doses and of subjects reporting each solicited AE including those graded "3" in intensity and those assessed as related to vaccination during the 8-day (Day 0 – Day 7) follow-up period for all doses.

- From Day 0 to Day 7 after any HRV vaccine/placebo doses, the percentage of subjects with reports of solicited AEs including those rated as grade "3" and those assessed as related to vaccination were similar in both groups.
- Irritability was the most frequently reported solicited AE after each dose in both groups; reported for 51.4% subjects in the HRV group and 48.6% subjects in the placebo group (Table 27 and Supplement 44).
- Grade "3" solicited AEs were reported in less than 2.0% of the subjects after each dose in both groups (Table 27).

Table 27 Percentage of subjects reporting each solicited general symptom including those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period, for each dose (Total vaccinated cohort)

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
Cough/runny nose	All	508	110	21.7	18.1	25.5	257	64	24.9	19.7	30.7
	Grade 3	508	2	0.4	0.0	1.4	257	1	0.4	0.0	2.1
	Related	508	4	0.8	0.2	2.0	257	1	0.4	0.0	2.1
Diarrhoea	All	508	26	5.1	3.4	7.4	257	8	3.1	1.4	6.0
	Grade 3	508	6	1.2	0.4	2.6	257	1	0.4	0.0	2.1
	Related	508	10	2.0	0.9	3.6	257	3	1.2	0.2	3.4
Fever	All	508	38	7.5	5.3	10.1	257	12	4.7	2.4	8.0
	Grade 3	508	1	0.2	0.0	1.1	257	0	0.0	0.0	1.4
	Related	508	3	0.6	0.1	1.7	257	0	0.0	0.0	1.4
Irritability	All	508	200	39.4	35.1	43.8	257	93	36.2	30.3	42.4
	Grade 3	508	9	1.8	0.8	3.3	257	3	1.2	0.2	3.4
	Related	508	18	3.5	2.1	5.5	257	11	4.3	2.2	7.5
Loss of appetite	All	508	50	9.8	7.4	12.8	257	18	7.0	4.2	10.8
	Grade 3	508	1	0.2	0.0	1.1	257	0	0.0	0.0	1.4
	Related	508	3	0.6	0.1	1.7	257	1	0.4	0.0	2.1
Vomiting	All	508	58	11.4	8.8	14.5	257	28	10.9	7.4	15.4
	Grade 3	508	9	1.8	0.8	3.3	257	2	0.8	0.1	2.8
	Related	508	3	0.6	0.1	1.7	257	1	0.4	0.0	2.1
Dose 2											
Cough/runny nose	All	499	127	25.5	21.7	29.5	250	49	19.6	14.9	25.1
	Grade 3	499	0	0.0	0.0	0.7	250	0	0.0	0.0	1.5
	Related	499	16	3.2	1.8	5.2	250	1	0.4	0.0	2.2
Diarrhoea	All	499	23	4.6	2.9	6.8	250	8	3.2	1.4	6.2
	Grade 3	499	5	1.0	0.3	2.3	250	1	0.4	0.0	2.2
	Related	499	10	2.0	1.0	3.7	250	5	2.0	0.7	4.6
Fever	All	499	33	6.6	4.6	9.2	250	12	4.8	2.5	8.2
	Grade 3	499	2	0.4	0.0	1.4	250	0	0.0	0.0	1.5
	Related	499	4	0.8	0.2	2.0	250	0	0.0	0.0	1.5
Irritability	All	499	157	31.5	27.4	35.7	250	77	30.8	25.1	36.9
	Grade 3	499	6	1.2	0.4	2.6	250	1	0.4	0.0	2.2
	Related	499	25	5.0	3.3	7.3	250	8	3.2	1.4	6.2
Loss of appetite	All	499	45	9.0	6.7	11.9	250	20	8.0	5.0	12.1
	Grade 3	499	0	0.0	0.0	0.7	250	0	0.0	0.0	1.5
	Related	499	7	1.4	0.6	2.9	250	1	0.4	0.0	2.2
Vomiting	All	499	32	6.4	4.4	8.9	250	14	5.6	3.1	9.2
	Grade 3	499	5	1.0	0.3	2.3	250	1	0.4	0.0	2.2
	Related	499	4	0.8	0.2	2.0	250	1	0.4	0.0	2.2

For each dose
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once the symptom

8.2.3. Unsolicited adverse events

Table 28 presents the percentage of subjects reporting the occurrence of unsolicited AEs classified by MedDRA SOC during the 31-day (Day 0 – Day 30) post vaccination period.

Table 29 presents the percentage of subjects reporting unsolicited AEs classified by MedDRA SOC with causal relationship to vaccination within the 31-day (Day 0 – Day 30) post vaccination period.

Table 30 presents the percentage of subjects with grade "3" unsolicited AEs classified by MedDRA SOC within the 31-day (Day 0 – Day 30) post vaccination period.

Supplement 45 presents the percentage of doses with unsolicited AEs classified by MedDRA SOC within the 31-day (Day 0 – Day 30) post vaccination period.

Supplement 46 presents the percentage of doses with unsolicited AEs classified by MedDRA SOC with causal relationship to vaccination within the 31-day (Day 0 – Day 30) post vaccination period.

Supplement 47 presents the percentage of doses with grade "3" unsolicited AEs classified by MedDRA SOC within the 31-day (Day 0 – Day 30) post vaccination period.

- The percentage of subjects with report of at least one unsolicited AE classified by MedDRA SOC was 54.9% in the HRV group and 56.0% in the placebo group.
- Unsolicited AEs assessed as causally related to vaccination were reported for 1.0% of the subjects in the HRV group and 0.8% of the subjects in the placebo group.
- The percentage of subjects with report of at least one grade "3" unsolicited AE classified by MedDRA SOC was 2.8% in the HRV group and 3.5% in the placebo group.

Table 28 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

	HRV N = 508				Placebo N = 257			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	279	54.9	50.5	59.3	144	56.0	49.7	62.2
Blood and lymphatic system disorders (10005329)	*1*				*1*			
Congenital, familial and genetic disorders (10010331)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
Ear and labyrinth disorders (10013993)	4	0.8	0.2	2.0	1	0.4	0.0	2.1
Eye disorders (10015919)	29	5.7	3.9	8.1	13	5.1	2.7	8.5
Gastrointestinal disorders (10017947)	38	7.5	5.3	10.1	21	8.2	5.1	12.2
General disorders and administration site conditions (10018065)	9	1.8	0.8	3.3	8	3.1	1.4	6.0
Hepatobiliary disorders (10019805)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
Infections and infestations (10021881)	116	22.8	19.3	26.7	59	23.0	18.0	28.6
Injury, poisoning and procedural complications (10022117)	4	0.8	0.2	2.0	6	2.3	0.9	5.0
Metabolism and nutrition disorders (10027433)	*1*				*1*			
Musculoskeletal and connective tissue disorders (10028395)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
Nervous system disorders (10029205)	*2*				*2*			
Psychiatric disorders (10037175)	*1*				*1*			
Respiratory, thoracic and mediastinal disorders (10038738)	67	13.2	10.4	16.4	41	16.0	11.7	21.0
Skin and subcutaneous tissue disorders (10040785)	136	26.8	23.0	30.8	55	21.4	16.5	26.9

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
n = n cases reported in one group and none in the other group. Those cases remain blinded as study is ongoing.

Table 29 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

	HRV N = 508				Placebo N = 257			
			95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom	5	1.0	0.3	2.3	2	0.8	0.1	2.8
Gastrointestinal disorders (10017947)	5	1.0	0.3	2.3	2	0.8	0.1	2.8

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 30 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

	HRV N = 508				Placebo N = 257			
			95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom	14	2.8	1.5	4.6	9	3.5	1.6	6.5
Gastrointestinal disorders (10017947)	*2*				*2*			
Hepatobiliary disorders (10019805)	*1*				*1*			
Infections and infestations (10021881)	8	1.6	0.7	3.1	6	2.3	0.9	5.0
Respiratory, thoracic and mediastinal disorders (10038738)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
Skin and subcutaneous tissue disorders (10040785)	2	0.4	0.0	1.4	1	0.4	0.0	2.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
n = n cases reported in one group and none in the other group. Those cases remain blinded as study is ongoing.

8.3. Serious adverse events

The serious adverse event (SAE) Summary Table(s) are in Section 14.1 and the SAE CIOMS are in Section 0.

Table 31 presents the percentage of subjects with SAEs classified by MedDRA SOC from Dose 1 up to the data lock point.

- From Dose 1 up to the data lock point, 13.6% of the subjects in the HRV group and 16.0% of the subjects in the placebo had report of at least one SAE.

Table 31 Percentage of subjects with SAEs classified by MedDRA system organ class from Dose 1 till database lock (Total vaccinated cohort)

	HRV N = 508				Placebo N = 257			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	69	13.6	10.7	16.9	41	16.0	11.7	21.0
Blood and lymphatic system disorders (10005329)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
Congenital, familial and genetic disorders (10010331)	*1*				*1*			
Gastrointestinal disorders (10017947)	8	1.6	0.7	3.1	3	1.2	0.2	3.4
General disorders and administration site conditions (10018065)	3	0.6	0.1	1.7	1	0.4	0.0	2.1
Hepatobiliary disorders (10019805)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
Infections and infestations (10021881)	54	10.6	8.1	13.6	30	11.7	8.0	16.2
Injury, poisoning and procedural complications (10022117)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
Metabolism and nutrition disorders (10027433)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
Musculoskeletal and connective tissue disorders (10028395)	*1*				*1*			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	*3*				*3*			
Nervous system disorders (10029205)	5	1.0	0.3	2.3	5	1.9	0.6	4.5
Psychiatric disorders (10037175)	*1*				*1*			
Respiratory, thoracic and mediastinal disorders (10038738)	6	1.2	0.4	2.6	2	0.8	0.1	2.8

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
n = n cases reported in one group and none in the other group. Those cases remain blinded as study is ongoing.
Data base lock date = 31MAR2009

8.3.1. Fatal events

There were no fatal events reported up to the data lock point.

8.3.2. Non-fatal events

Supplement 48 presents the listing of SAEs reported from Dose 1 up to the data lock point.

- A total of 159 SAEs were reported for 110 subjects from Dose 1 up to the data lock point. None of these SAEs were assessed to be causally related to vaccination.

8.4. Adverse events leading to premature discontinuation of study vaccine and/or study

[redacted] This medical condition developed 20 days after receiving Dose 2 and the randomisation code was broken. The screens for Visit 5 were not yet filled at the time of database freeze hence; further information on this subject is not yet available.

8.5. Concomitant medications

Supplement 49 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 vaccination by type in both groups.

Supplement 50 presents the number and percentage of doses and of subjects who started taking at least one concomitant medication during study period (from Dose 1 up to the data lock point) after vaccination.

- The percentage of subjects who started taking at least one concomitant medication from Day 0 to Day 7 was similar in both groups (28.0% [95% CI: 24.1%; 32.1%] in the HRV group and 24.9% [95% CI: 19.7%; 30.7%] in the placebo group).
- The percentage of subjects who started taking any antipyretic or any antibiotic from Dose 1 up to the data lock point was similar in both groups. Antibiotics were taken in a high percentage of subjects (29.9% [95% CI: 26.0%; 34.1%] in the HRV group and 25.3% [95% CI: 20.1%; 31.1%] in the placebo group).

8.6. Important safety information received after the database freeze date

There was no significant safety data received after the database freeze date for this study.

8.7. Safety conclusions

- There was no evidence of a clinically meaningful difference between the HRV group and placebo group for SAEs reported from Dose 1 up to the data lock point or unsolicited AEs reported during the 31-day (Day 0 – Day 30) follow-up period after any dose.
- The reactogenicity profile of two doses of HRV vaccine was similar to that of the placebo in terms of the solicited AEs reported during the 8-day (Day 0 – Day 7) follow-up period after each dose.

9. IMMUNOGENICITY RESULTS

9.1. Data sets analysed

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity.

9.2. According-to-protocol analysis

The ATP cohort for immunogenicity consisted of 54 subjects (34 subjects in the HRV group and 20 subjects in placebo group).

9.2.1. Serum anti-rotavirus IgA antibody response in the immunogenicity subset

Table 32 presents the anti-rotavirus IgA antibody GMCs and seroconversion rates for the subjects who were part of the immunogenicity subset.

Table 33 presents the anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies.

- The anti-rotavirus IgA antibody seroconversion rate was 85.3% [95% CI: 68.9%; 95.0%] in the HRV group and 5.0% [95% CI: 0.1%; 24.9%] in the placebo group at one month post Dose 2 of HRV vaccine/placebo.

- Anti-rotavirus IgA antibody GMCs calculated on seropositive subjects were 368.9 U/mL in the HRV group and 496.0 U/mL in the placebo group (only one subject was seropositive at Visit 3 in the placebo group).

- The lower limit of the two sided asymptotic standardised 95% CI for the difference in the percentage of subjects who seroconverted at Visit 3 between the HRV group and [minus] the placebo group was 57.98% indicating that the seroconversion rate was significantly higher in the HRV group compared to the placebo group.

Table 32 Anti-rotavirus IgA antibody GMC and seroconversion rates from a subset of subjects - ATP cohort for immunogenicity

			≥ 20 U/mL				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV	PRE	34	0	0.0	0.0	10.3	<20	-	-
	PII(M2)	34	29	85.3	68.9	95.0	217.0	109.9	428.6
Placebo	PRE	20	0	0.0	0.0	16.8	<20	-	-
	PII(M2)	20	1	5.0	0.1	24.9	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration ≥ 20 U/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M2) = One month after the second dose (Visit 3)
PRE = pre-vaccination

Table 33 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies at Visit 3 from a subset of subjects - ATP cohort for immunogenicity

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV	PII(M2)	29	368.9	202.1	673.3
Placebo	PII(M2)	1	496.0	-	-

GMC = geometric mean antibody concentration calculated on subjects with concentration ≥ 20 U/mL
N = number of subjects who seroconverted for Anti-rotavirus IgA Antibody
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII (M2) = One month after the second dose (Visit 3)

Table 34 Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum anti-rotavirus IgA antibody from a subset of subjects - ATP cohort for immunogenicity

						Difference in seroconversion rate			
							value	95 % CI	
Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HRV	34	85.3	Placebo	20	5.0	HRV - Placebo	80.29	57.98	90.89

N = number of subjects with available results
% = percentage of subjects who seroconverted at Visit 3
95% CI = 95% Standardised asymptotic confidence interval; LL = lower limit, UL = upper limit

Supplement 51 presents the RCCs for anti-rotavirus IgA antibody concentrations at Visit 3.

9.3. Immunogenicity conclusion

- Two doses of the HRV vaccine were immunogenic as shown by the anti-rotavirus IgA antibody seroconversion rate of 85.3% [95% CI: 68.9%; 95.0%] in the HRV group at one month post Dose 2 of the HRV vaccine.

10. DISCUSSION AND OVERALL CONCLUSIONS

10.1. Discussion

This phase III, double-blind, randomised, placebo-controlled study was conducted in Japan to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of GSK Biologicals' HRV vaccine in healthy infants previously uninfected with HRV.

In this study, RV GE was defined as an episode of any GE leading to medical intervention occurring at least 2 weeks post Dose 2 in which RV other than the vaccine strain was identified in a stool sample collected. It was decided prior to the start of the study that final analyses would be performed when 28 RV GE cases leading to medical intervention and caused by the circulating wild-type strains were identified or when all subjects had reached 2 years of age whichever was the earliest. Since the required number of RV GE cases leading to medical intervention were identified, final analyses was performed on the efficacy, reactogenicity, safety and immunogenicity up to the data lock point of 31 March 2009. The efficacy and safety data up to 2 years of age will be presented in an annex report. The duration of the efficacy follow-up period from 2 weeks post Dose 2 up to the data lock point for the ATP cohort for efficacy was 1.31 years in both groups.

Two doses of the HRV vaccine were very efficacious against any RV GE leading to medical intervention with a vaccine efficacy of 81.9% [95% CI: 60.0%; 92.6%] and was comparable to the vaccine efficacy results obtained in a previous study conducted in Europe (83.8% [95% CI: 76.8%; 88.9%]) [Vesikari, 2007]. The vaccine efficacy against severe RV GE episodes leading to medical intervention (95.4% [95% CI: 68.6%; 99.9%]) similar to those observed in previous studies conducted in Europe (90.4% [95% CI: 85.1%; 94.1%]) and Asia (96.1% [95% CI: 85.1%; 99.5%]) [Vesikari, 2007;Phua, 2009]. There were few reports of hospitalisation due to RV GE (1 subject in each group). Exploratory analysis performed using the Cox model showed that a total of 6.6 any RV GE episodes leading to medical intervention and 3.2 severe RV GE episodes leading to medical intervention per 100 infant year could be prevented by vaccination.

The most predominant strains isolated during the study period up to the data lock point were G3P[8] and G1P[8]. Vaccine efficacy observed against G1 wild-type leading to medical intervention was 91.6% [95% CI: 31.0%; 99.8%] and against non-G1 types leading to medical intervention was 78.9% [95% CI: 49.4%; 92.0%]. High vaccine efficacy was also observed against severe RV GE leading to medical intervention caused by G1 wild-type RV (100% [95% CI: 24.0%; 100.0%]) and non-G1 types leading to medical intervention (92.8% [95% CI: 44.2%; 99.8%]). Significant protection was shown against G3 type (87.4% [95% CI: 53.5%; 97.7%]). However, low incidence of G2, G4 and G9 types precluded demonstration of statistical significance against these types.

There were very few cases of hospitalised RV GE (one subject in each group) in this study. This might be due to the medical attention seeking behaviour of the Japanese parents. Seeking medical attention early and easy access to medical care would reduce the number of hospitalisations. Nevertheless, Nakagomi et al [Nakagomi, 2005] estimated that the incidence of rotavirus disease associated hospitalisations among

children <5 years of age was 7.9 – 17.6 hospitalisations/1000 person-years, and the estimated cumulative incidence by 5 years of age was 6.6%. Thus, approximately 1 in 15 children will require hospitalisation due to rotavirus diarrhoea by their fifth year of life. In Japan, this would mean that 78,000 children <5 years of age would be hospitalised each year, resulting in a direct medical cost of 10 billion yen (96 US dollars million). The burden associated with RV GE in Japan is substantial and might be reduced through the introduction of vaccines.

The immune response to the HRV vaccine was evaluated only in a subset of subjects (N = 54). Two oral doses of the HRV vaccine were highly immunogenic with anti-rotavirus IgA antibody seroconversion rate of 85.3% [95% CI: 68.9%; 95.0%] observed in the HRV group at one month post Dose 2. The seroconversion rate was comparable to those in previous studies (86.5% [95% CI: 83.9%; 88.8%] and 93.9% [95% CI: 87.9%; 97.5%]) [Vesikari, 2006; Quak, 2005].

It was interesting to note that none of the subjects enrolled in this study were seropositive prior to the start of the study. In Japan, most of the RV infections occur between January and June with the peak being in March. The subjects (mean age of 7.7 weeks) were enrolled between 19 June 2007 and 29 December 2007 thus clearly indicating that most of the subjects were born after the peak RV season in 2007 and the pre-vaccination blood samples were taken prior to the next RV season.

As observed in previous studies [Vesikari, 2004; Vesikari, 2004; Salinas, 2005], the reactogenicity and safety profile was similar in both groups. Since the study is still ongoing, the adverse events reported were only analysed according to MedDRA SOC to maintain blinding. A total of 159 SAEs were reported for 110 subjects from Dose 1 up to the data lock point. However, none of these SAEs were assessed to be causally related to vaccination. There were no fatal cases in the study. Overall, there was no clinically relevant safety concern raised based on the available safety data.

10.2. Overall conclusions

Efficacy

- Two oral doses of GSK Biologicals' HRV vaccine were highly efficacious in preventing any RV GE leading to medical intervention caused by circulating wild-type RV strains during the period starting from 2 weeks post Dose 2 up to the data lock point with a vaccine efficacy of 81.9% [95% CI: 60.0%; 92.6%]. The primary objective of this study was met.
- Two oral doses of the HRV vaccine were efficacious during the period starting from 2 weeks post Dose 2 up to the data lock point in protecting infants against:
- Severe RV GE leading to medical intervention caused by the circulating wild-type RV with a vaccine efficacy of 95.4% [95% CI: 68.6%; 99.9%].
- Any RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].

  - Severe RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 100% [95% CI: 24.0%; 100.0%].
  - Any RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 78.9% [95% CI: 49.4%; 92.0%].
  - Severe RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 92.8% [95% CI: 44.2%; 99.8%].
  - There were few reports of hospitalisation due to RV GE (1 subject in each group).

- During the period starting from Dose 1 up to the data lock point, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 82.5% [95% CI: 61.4%; 92.8%] and 95.8% [95% CI: 71.5%: 99.9%], respectively.

Reactogenicity and Safety

- There was no evidence of a clinically meaningful difference between the HRV group and placebo group for SAEs reported from Dose 1 up to the data lock point or unsolicited AEs reported during the 31-day (Day 0 – Day 30) follow-up period after any dose.
- The reactogenicity profile of two doses of HRV vaccine was similar to that of the placebo in terms of the solicited AEs reported during the 8-day (Day 0 – Day 7) follow-up period after each dose.

Immunogenicity

- Two doses of the HRV vaccine were immunogenic as shown by the anti-rotavirus IgA antibody seroconversion rate of 85.3% [95% CI: 68.9%; 95.0%] in the HRV group at one month post Dose 2 of the HRV vaccine.

11. SUPPLEMENTS

Supplement 1 Minimum and maximum activity dates (Total vaccinated cohort)

Visit	Minimum date	Maximum date
1	19JUN2007	29DEC2007
2	24JUL2007	08FEB2008
3	24AUG2007	18MAR2008
4	25MAR2008	22NOV2008
5	24MAR2009	31MAR2009*

*Database Lock Date = 31MAR2009

Supplement 2 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Visit 4 – First year conclusion (Total vaccinated cohort)

	HRV	Placebo	Total
Number of subjects vaccinated	508	257	765
Number of subjects completed	492	247	739
Number of subjects withdrawn	16	10	26
Reasons for withdrawal :			
Serious Adverse Event	1	0	1
Non-serious adverse event	0	1	1
Protocol violation	0	1	1
Consent withdrawal (not due to an adverse event)	9	3	12
Migrated/moved from study area	6	2	8
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	3	3

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed Visit 4
Withdrawn = number of subjects who did not come for Visit 4

Supplement 3 Deviations from specifications for age and intervals between study visits (Total vaccinated cohort)

		Age	PRE-Dose:1	Dose:1-Dose:2		Dose:2-PII(M2)	
Group		Protocol	Protocol	Protocol	Adapted	Protocol	Adapted
		from 6 to 14 weeks	from 0 to 0 days	from 30 to 48 days	from 21 to 48 days	from 30 to 48 days	from 21 to 48 days
HRV	N	508	37	499	499	35	35
	n	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0
	range	6 to 14	0 to 0	30 to 47	30 to 47	30 to 45	30 to 45
Placebo	N	257	20	250	250	20	20
	n	1	0	0	0	0	0
	%	0.4	0.0	0.0	0.0	0.0	0.0
	range	5 to 14	0 to 0	30 to 47	30 to 47	30 to 42	30 to 42

Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n (%) = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals
PRE = pre-vaccination
PII(M2) = One month after the second dose (Visit 3)

Supplement 4 Deviations from specifications for age and intervals between study visits (ATP cohort for immunogenicity)

		Age	PRE-Dose:1	Dose:1-Dose:2		Dose:2-PII(M2)	
Group		**Protocol**	**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 6 to 14 weeks	from 0 to 0 days	from 30 to 48 days	from 21 to 48 days	from 30 to 48 days	from 21 to 48 days
HRV	N	34	34	34	34	34	34
	n	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0
	range	6 to 12	0 to 0	30 to 42	30 to 42	32 to 45	32 to 45
Placebo	N	20	20	20	20	20	20
	n	0	0	0	0	0	0
	%	0.0	0.0	0.0	0.0	0.0	0.0
	range	6 to 10	0 to 0	30 to 44	30 to 44	30 to 42	30 to 42

Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results
n (%) = number / percentage of subjects with results outside of the interval
range = minimum-maximum for age and intervals
PRE = pre-vaccination
PII(M2) = One month after the second dose (Visit 3)

Supplement 5 Summary of feeding practices at Dose 1, at Dose 2 of HRV vaccine or Placebo (ATP cohort for efficacy)

		HRV			Placebo			Total		
DOSE	**Parameters or Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Dose 1	Breast-fed	498	310	62.2	250	154	61.6	748	464	62.0
	Formula-fed	498	38	7.6	250	15	6.0	748	53	7.1
	Solid-food	498	0	0.0	250	0	0.0	748	0	0.0
	Breast-fed and Formula-fed	498	150	30.1	250	81	32.4	748	231	30.9
	Breast-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Formula-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Breast-fed Formula-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
Dose 2	Breast-fed	498	325	65.3	250	159	63.6	748	484	64.7
	Formula-fed	498	50	10.0	250	23	9.2	748	73	9.8
	Solid-food	498	0	0.0	250	0	0.0	748	0	0.0
	Breast-fed and Formula-fed	498	120	24.1	250	68	27.2	748	188	25.1
	Breast-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Formula-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Breast-fed Formula-fed and Solid food	498	3	0.6	250	0	0.0	748	3	0.4
Combined dose	Breast-fed	498	291	58.4	250	144	57.6	748	435	58.2
	Formula-fed	498	34	6.8	250	15	6.0	748	49	6.6
	Solid-food	498	0	0.0	250	0	0.0	748	0	0.0
	Breast-fed and Formula-fed	498	102	20.5	250	58	23.2	748	160	21.4
	Breast-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Formula-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Breast-fed Formula-fed and Solid food	498	0	0.0	250	0	0.0	748	0	0.0
	Other	498	71	14.3	250	33	13.2	748	104	13.9

For each dose: N = number of subjects who received the considered dose
For Combined dose: N= number of subjects who received two dose
n (%)=number (percentage) of subjects with the specified feeding criteria
Combined = Feeding practices at both the doses
Other= the subjects who have not had the same feeding type at both the doses

Supplement 6 Summary of demographic characteristics (Total vaccinated cohort)

		HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at Dose 1 of HRV/placebo	Mean	7.7	-	7.7	-	7.7	-
	SD	1.99	-	2.05	-	2.01	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	5	-	5	-
	Maximum	14	-	14	-	14	-
Age (weeks) at Dose 2 of HRV/placebo	Mean	12.7	-	12.7	-	12.7	-
	SD	2.03	-	2.18	-	2.08	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	19	-	20	-	20	-
	Unknown	9	-	7	-	16	-
Age (months) at database lock(31MAR2009)/ at the last contact	Mean	18.4	-	18.2	-	18.3	-
	SD	2.69	-	3.07	-	2.82	-
	Median	19.0	-	18.0	-	19.0	-
	Minimum	1	-	2	-	1	-
	Maximum	24	-	23	-	24	-
Gender	Female	229	45.1	134	52.1	363	47.5
	Male	279	54.9	123	47.9	402	52.5
Race	African heritage / African American	0	-	0	-	0	-
	American Indian or Alaskan native	0	-	0	-	0	-
	Asian - Central/South Asian heritage	0	-	0	-	0	-
	Asian - East Asian heritage	0	-	0	-	0	-
	Asian - Japanese heritage	508	100	257	100	765	100
	Asian - South east Asian heritage	0	-	0	-	0	-
	Native Hawaiian or other pacific Islande	0	-	0	-	0	-
	White - Arabic / North African heritage	0	-	0	-	0	-
	White - Caucasian / European heritage	0	-	0	-	0	-
	Other	0	-	0	-	0	-
Height (cm) at Visit 1	Mean	56.5	-	56.4	-	56.5	-
	SD	2.75	-	2.74	-	2.75	-
	Median	56.0	-	56.0	-	56.0	-
Weight (kg) at Visit 1	Mean	5.2	-	5.1	-	5.1	-
	SD	0.76	-	0.71	-	0.74	-
	Median	5.1	-	5.0	-	5.1	-

N = total number of subjects in each group
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
Unknown = Subjects who did not receive second dose of HRV/Placebo
Database Lock Date = 31MAR2009

Supplement 7 Summary of feeding practices at Dose 1 and at Dose 2 of HRV vaccine or Placebo (Total vaccinated cohort)

		HRV			Placebo			Total		
DOSE	**Parameters or Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Dose 1	Breast-fed	508	316	62.2	257	158	61.5	765	474	62.0
	Formula-fed	508	39	7.7	257	15	5.8	765	54	7.1
	Solid-food	508	0	0.0	257	0	0.0	765	0	0.0
	Breast-fed and Formula-fed	508	153	30.1	257	84	32.7	765	237	31.0
	Breast-fed and Solid food	508	0	0.0	257	0	0.0	765	0	0.0
	Formula-fed and Solid food	508	0	0.0	257	0	0.0	765	0	0.0
	Breast-fed Formula-fed and Solid food	508	0	0.0	257	0	0.0	765	0	0.0
Dose 2	Breast-fed	499	326	65.3	250	159	63.6	749	485	64.8
	Formula-fed	499	50	10.0	250	23	9.2	749	73	9.7
	Solid-food	499	0	0.0	250	0	0.0	749	0	0.0
	Breast-fed and Formula-fed	499	120	24.0	250	68	27.2	749	188	25.1
	Breast-fed and Solid food	499	0	0.0	250	0	0.0	749	0	0.0
	Formula-fed and Solid food	499	0	0.0	250	0	0.0	749	0	0.0
	Breast-fed Formula-fed and Solid food	499	3	0.6	250	0	0.0	749	3	0.4
Combined Dose	Breast-fed	499	292	58.5	250	144	57.6	749	436	58.2
	Formula-fed	499	34	6.8	250	15	6.0	749	49	6.5
	Solid-food	499	0	0.0	250	0	0.0	749	0	0.0
	Breast-fed and Formula-fed	499	102	20.4	250	58	23.2	749	160	21.4
	Breast-fed and Solid food	499	0	0.0	250	0	0.0	749	0	0.0
	Formula-fed and Solid food	499	0	0.0	250	0	0.0	749	0	0.0
	Breast-fed Formula-fed and Solid food	499	0	0.0	250	0	0.0	749	0	0.0
	Other	499	71	14.2	250	33	13.2	749	104	13.9

For each dose: N = number of subjects who received the considered dose
For Combined dose: N= number of subjects who received two dose
n(%)=number(percentage) of subjects with the specified feeding criteria
Combined = Feeding practices at both the doses
Other= The subjects who have not had the same feeding type at both the doses

Supplement 8 Subjects unblinded before database lock (31MAR2009) (Total vaccinated cohort)

Group	Subject number	Date of unblinding	Previous dose	Day of onset	Reason
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 9 Summary of demographic characteristics (ATP cohort for Immunogenicity)

		HRV N = 34		Placebo N = 20		Total N = 54	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at Dose 1 of HRV/placebo	Mean	7.5	-	7.2	-	7.4	-
	SD	1.60	-	1.23	-	1.47	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	6	-	6	-
	Maximum	12	-	10	-	12	-
Age (weeks) at Dose 2 of HRV/placebo	Mean	12.7	-	12.0	-	12.4	-
	SD	1.57	-	1.45	-	1.55	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	11	-	10	-	10	-
	Maximum	17	-	15	-	17	-
Age (months) at database lock(31MAR2009)/ at the last contact	Mean	19.4	-	19.6	-	19.5	-
	SD	2.12	-	1.96	-	2.04	-
	Median	20.0	-	20.0	-	20.0	-
	Minimum	12	-	16	-	12	-
	Maximum	22	-	22	-	22	-
Gender	Female	14	41.2	14	70.0	28	51.9
	Male	20	58.8	6	30.0	26	48.1
Race	African heritage / African American	0	-	0	-	0	-
	American Indian or Alaskan native	0	-	0	-	0	-
	Asian - Central/South Asian heritage	0	-	0	-	0	-
	Asian - East Asian heritage	0	-	0	-	0	-
	Asian - Japanese heritage	34	100	20	100	54	100
	Asian - South east Asian heritage	0	-	0	-	0	-
	Native Hawaiian or other Pacific Islande	0	-	0	-	0	-
	White - Arabic / North African heritage	0	-	0	-	0	-
	White - Caucasian / European heritage	0	-	0	-	0	-
	Other	0	-	0	-	0	-
Height (cm)	Mean	55.3	-	55.7	-	55.5	-
	SD	3.80	-	1.87	-	3.21	-
	Median	55.5	-	55.0	-	55.0	-
Weight (kg)	Mean	5.2	-	5.1	-	5.1	-
	SD	0.66	-	0.49	-	0.60	-
	Median	5.1	-	5.2	-	5.2	-

N = total number of subjects in each group
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
Database Lock Date = 31MAR2009

Supplement 10 Summary of Co-administered vaccination by dose (Total vaccinated cohort)

	HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Dose 1						
Any	17	3.3	6	2.3	23	3.0
DTPa	17	3.3	6	2.3	23	3.0
Dose 2						
Any	21	4.2	11	4.4	32	4.3
DTPa	20	4.0	10	4.0	30	4.0
HBV	1	0.2	1	0.4	2	0.3

N = Total number of subjects having recieved the considered dose of HRV/Placebo
n (%)=number (percentage) who recieved specified vaccination on the same day as the considered dose of HRV/placebo

Supplement 11 Summary of vaccinations other than HRV/Placebo administered during the study period, excluding vaccination given on the day of HRV/placebo (Total vaccinated cohort)

Before Dose 1									
	HRV N = 508			Placebo N = 257			Total N = 765		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**
Any	1	1	0.2	4	3	1.2	5	4	0.5
DTPa	1	1	0.2	2	2	0.8	3	3	0.4
HBV	*1*	*1*		*1*	*1*		*1*	*1*	
Between Dose 1 and Dose 2§									
	HRV N = 508			Placebo N = 257			Total N = 765		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**
Any	21	19	3.7	10	8	3.1	31	27	3.5
BCG	1	1	0.2	2	2	0.8	3	3	0.4
DTPa	20	19	3.7	7	6	2.3	27	25	3.3
HBV	*1*	*1*		*1*	*1*		*1*	*1*	
Between Dose 2 and visit 3£									
	HRV N = 499			Placebo N = 250			Total N = 749		
Characteristics	**#**	**N**	**%**	**#**	**n**	**%**	**#**	**N**	**%**
Any	278	206	41.3	135	99	39.6	413	305	40.7
BCG	138	138	27.7	68	68	27.2	206	206	27.5
DTPa	138	111	22.2	66	53	21.2	204	164	21.9
HBV	*1*	*1*		*1*	*1*		*1*	*1*	
OPV	1	1	0.2	1	1	0.4	2	2	0.3

N = Before Dose 1 and between Dose 1 and Dose 2 : total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV/placebo
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV/placebo doses
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 3 if dose 2 of HRV/placebo was not administered
£= up to last contact of conclusion at Visit 3 if visit 3 was not done
n = n cases reported in one group and none in the other group. Those cases remain blinded as study is ongoing.

Supplement 12 Percentage of subjects with RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, by G type and P type - ATP cohort for efficacy

	HRV N = 498		Placebo N = 250	
Serotype	n	%	n	%
Any	9	1.8	25	10.0
G1 wild type	1	0.2	6	2.4
G2	1	0.2	1	0.4
G3	3	0.6	12	4.8
G4	1	0.2	1	0.4
G9	3	0.6	5	2.0
P4	1	0.2	1	0.4
P8 wild type	8	1.6	24	9.6

N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified serotype in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the serotype
Database Lock date = 31MAR2009

Supplement 13 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, by G type and P type - ATP cohort for efficacy

	HRV N = 498		Placebo N = 250		Total N = 748	
Serotype	n	%	n	%	n	%
Any	1	0.2	11	4.4	12	1.6
G1 wild type	0	0.0	4	1.6	4	0.5
G3	0	0.0	5	2.0	5	0.7
G9	1	0.2	2	0.8	3	0.4
P8 wild type	1	0.2	11	4.4	12	1.6

N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified serotype in each group
Any = number of subjects reporting at least one severe rotavirus gastroenteritis episodes, whatever is the serotype
Database Lock date = 31MAR2009

Supplement 14 Number of RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy

Serotype	HRV N'= 9		Placebo N'= 25	
	n	%	n	%
G1WT+P8WT	1	11.11	6	24.00
G2+P4	1	11.11	1	4.00
G3+P8WT	3	33.33	12	48.00
G4+P8WT	1	11.11	1	4.00
G9+P8WT	3	33.33	5	20.00

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
Database lock date = 31MAR2009

Supplement 15 Characteristics (based on the Vesikari scale) of severe RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to database lock, overall – ATP cohort for efficacy

		HRV N' = 1		Placebo N' = 11	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	20.0	-	12.6	-
	SD	0.0	-	1.6	-
	Median	20.0	-	12.0	-
	Minimum	20.0	-	11.0	-
	Maximum	20.0	-	15.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	3	27.3
	5	0	0.0	3	27.3
	more than 5 days	1	100	5	45.5
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	0	0.0	1	9.1
	more than 5	1	100	10	90.9
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	0	0.0	2	18.2
	2 days	0	0.0	4	36.4
	more than 2 days	1	100	5	45.5
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	0	0.0	2	18.2
	2 to 4	0	0.0	6	54.5
	more than 4	1	100	3	27.3
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	0	0.0	3	27.3
	38.5 to 38.9°C	0	0.0	1	9.1
	more than 38.9°C	1	100	7	63.6
Treatment	none	0	0.0	6	54.5
	rehydration	0	0.0	4	36.4
	hospitalisation	1	100	1	9.1
Dehydration	none	0	0.0	10	90.9
	1 to 5%	0	0.0	0	0.0
	more than 5 %	1	100	1	9.1

N' = number of severe RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 16 Characteristics (based on the Vesikari scale) of severe RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to database lock, by G9 – ATP cohort for efficacy

		HRV N' = 1		Placebo N' = 2	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	20.0	-	12.5	-
	SD	0.0	-	2.1	-
	Median	20.0	-	12.5	-
	Minimum	20.0	-	11.0	-
	Maximum	20.0	-	14.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	1	50.0
	5	0	0.0	0	0.0
	more than 5 days	1	100	1	50.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	0	0.0	1	50.0
	more than 5	1	100	1	50.0
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	0	0.0	0	0.0
	2 days	0	0.0	1	50.0
	more than 2 days	1	100	1	50.0
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	0	0.0	0	0.0
	2 to 4	0	0.0	1	50.0
	more than 4	1	100	1	50.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	0	0.0	1	50.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	1	100	1	50.0
Treatment	none	0	0.0	0	0.0
	rehydration	0	0.0	2	100
	hospitalisation	1	100	0	0.0
Dehydration	none	0	0.0	2	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	1	100	0	0.0

N' = number of severe RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 17 Characteristics (based on the Vesikari scale) of any RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, overall – ATP cohort for efficacy

		HRV N' = 9		Placebo N' = 25	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	8.1	-	9.5	-
	SD	4.7	-	3.3	-
	Median	6.0	-	9.0	-
	Minimum	5.0	-	4.0	-
	Maximum	20.0	-	15.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	3	33.3	10	40.0
	5	1	11.1	3	12.0
	more than 5 days	5	55.6	12	48.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	1	11.1	3	12.0
	4 to 5	4	44.4	7	28.0
	more than 5	4	44.4	15	60.0
Duration of vomiting (days)	0 day	7	77.8	9	36.0
	1 day	0	0.0	4	16.0
	2 days	0	0.0	6	24.0
	more than 2 days	2	22.2	6	24.0
Max number of episodes of vomiting /day	0	7	77.8	9	36.0
	1	1	11.1	5	20.0
	2 to 4	0	0.0	8	32.0
	more than 4	1	11.1	3	12.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	2	8.0
	37.1 to 38.4°C	5	55.6	11	44.0
	38.5 to 38.9°C	2	22.2	2	8.0
	more than 38.9°C	2	22.2	10	40.0
Treatment	none	6	66.7	17	68.0
	rehydration	2	22.2	7	28.0
	hospitalisation	1	11.1	1	4.0
Dehydration	none	8	88.9	23	92.0
	1 to 5%	0	0.0	1	4.0
	more than 5 %	1	11.1	1	4.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 18 Characteristics (based on the Vesikari scale) of any RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, G1WT – ATP cohort for efficacy

		HRV N' = 1		Placebo N' = 6	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	6.0	-	9.7	-
	SD	0.0	-	3.8	-
	Median	6.0	-	11.0	-
	Minimum	6.0	-	4.0	-
	Maximum	6.0	-	14.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	100	3	50.0
	5	0	0.0	2	33.3
	more than 5 days	0	0.0	1	16.7
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	1	16.7
	4 to 5	0	0.0	0	0.0
	more than 5	1	100	5	83.3
Duration of vomiting (days)	0 day	1	100	2	33.3
	1 day	0	0.0	1	16.7
	2 days	0	0.0	1	16.7
	more than 2 days	0	0.0	2	33.3
Max number of episodes of vomiting /day	0	1	100	2	33.3
	1	0	0.0	0	0.0
	2 to 4	0	0.0	3	50.0
	more than 4	0	0.0	1	16.7
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	16.7
	37.1 to 38.4°C	0	0.0	0	0.0
	38.5 to 38.9°C	1	100	1	16.7
	more than 38.9°C	0	0.0	4	66.7
Treatment	none	1	100	6	100
	rehydration	0	0.0	0	0.0
	hospitalisation	0	0.0	0	0.0
Dehydration	none	1	100	6	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 19 Characteristics (based on the Vesikari scale) of any RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, G2 type– ATP cohort for efficacy

		HRV N' = 1		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	10.0	-	9.0	-
	SD	0.0	-	0.0	-
	Median	10.0	-	9.0	-
	Minimum	10.0	-	9.0	-
	Maximum	10.0	-	9.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	0	0.0
	5	0	0.0	0	0.0
	more than 5 days	1	100	1	100
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	1	100
	more than 5	0	0.0	0	0.0
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	0	0.0	0	0.0
	2 days	0	0.0	0	0.0
	more than 2 days	1	100	1	100
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	1	100	1	100
	2 to 4	0	0.0	0	0.0
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	100
	37.1 to 38.4°C	1	100	0	0.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	0	0.0
Treatment	none	1	100	1	100
	rehydration	0	0.0	0	0.0
	hospitalisation	0	0.0	0	0.0
Dehydration	none	1	100	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 20 Characteristics (based on the Vesikari scale) of any RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, G3 type– ATP cohort for efficacy

		HRV N' = 3		Placebo N' = 12	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	6.0	-	9.8	-
	SD	0.0	-	3.4	-
	Median	6.0	-	9.5	-
	Minimum	6.0	-	5.0	-
	Maximum	6.0	-	15.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	33.3	3	25.0
	5	0	0.0	1	8.3
	more than 5 days	2	66.7	8	66.7
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	1	33.3	1	8.3
	4 to 5	2	66.7	3	25.0
	more than 5	0	0.0	8	66.7
Duration of vomiting (days)	0 day	3	100	4	33.3
	1 day	0	0.0	2	16.7
	2 days	0	0.0	4	33.3
	more than 2 days	0	0.0	2	16.7
Max number of episodes of vomiting /day	0	3	100	4	33.3
	1	0	0.0	3	25.0
	2 to 4	0	0.0	4	33.3
	more than 4	0	0.0	1	8.3
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	2	66.7	8	66.7
	38.5 to 38.9°C	0	0.0	1	8.3
	more than 38.9°C	1	33.3	3	25.0
Treatment	none	2	66.7	8	66.7
	rehydration	1	33.3	3	25.0
	hospitalisation	0	0.0	1	8.3
Dehydration	none	3	100	11	91.7
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	1	8.3

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 21 Characteristics (based on the Vesikari scale) of any RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, G9 type– ATP cohort for efficacy

		HRV N' = 3		Placebo N' = 5	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	11.0	-	8.8	-
	SD	7.9	-	3.6	-
	Median	8.0	-	7.0	-
	Minimum	5.0	-	6.0	-
	Maximum	20.0	-	14.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	33.3	4	80.0
	5	1	33.3	0	0.0
	more than 5 days	1	33.3	1	20.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	1	20.0
	4 to 5	0	0.0	3	60.0
	more than 5	3	100	1	20.0
Duration of vomiting (days)	0 day	2	66.7	2	40.0
	1 day	0	0.0	1	20.0
	2 days	0	0.0	1	20.0
	more than 2 days	1	33.3	1	20.0
Max number of episodes of vomiting /day	0	2	66.7	2	40.0
	1	0	0.0	1	20.0
	2 to 4	0	0.0	1	20.0
	more than 4	1	33.3	1	20.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	33.3	3	60.0
	38.5 to 38.9°C	1	33.3	0	0.0
	more than 38.9°C	1	33.3	2	40.0
Treatment	none	1	33.3	1	20.0
	rehydration	1	33.3	4	80.0
	hospitalisation	1	33.3	0	0.0
Dehydration	none	2	66.7	4	80.0
	1 to 5%	0	0.0	1	20.0
	more than 5 %	1	33.3	0	0.0

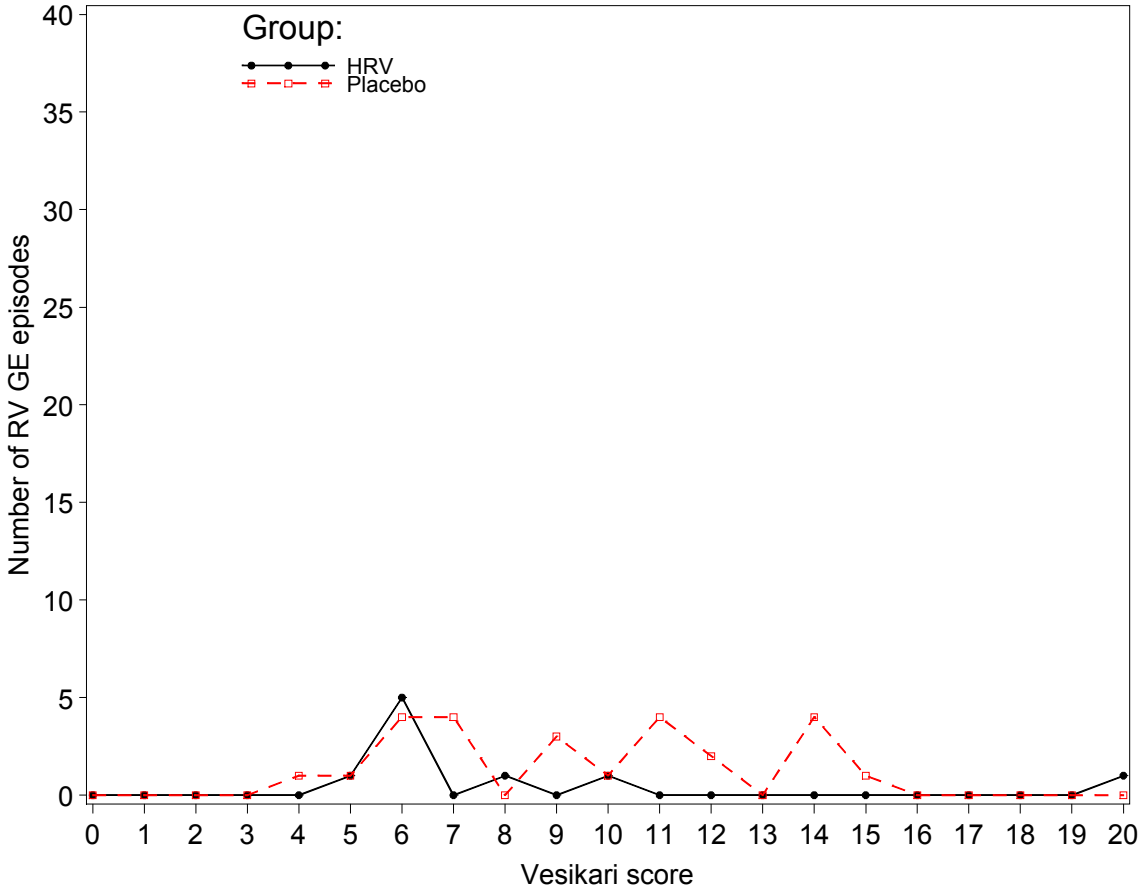
N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 22 Characteristics (based on the Vesikari scale) of any RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock, G4 type– ATP cohort for efficacy

		HRV N' = 1		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	6.0	-	9.0	-
	SD	0.0	-	0.0	-
	Median	6.0	-	9.0	-
	Minimum	6.0	-	9.0	-
	Maximum	6.0	-	9.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	0	0.0
	5	0	0.0	0	0.0
	more than 5 days	1	100	1	100
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	0	0.0
	more than 5	0	0.0	1	100
Duration of vomiting (days)	0 day	1	100	1	100
	1 day	0	0.0	0	0.0
	2 days	0	0.0	0	0.0
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	1	100	1	100
	1	0	0.0	0	0.0
	2 to 4	0	0.0	0	0.0
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	100	0	0.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	1	100
Treatment	none	1	100	1	100
	rehydration	0	0.0	0	0.0
	hospitalisation	0	0.0	0	0.0
Dehydration	none	1	100	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation
Database lock date = 31MAR2009

Supplement 23 Distribution of Vesikari score for RV GE episodes leading to medical intervention reported from 2 weeks after dose 2 up to database lock – ATP cohort for Efficacy



Supplement 24 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

Duration (years) of follow-up period	HRV N = 498	Placebo N = 250
	Value or n	Value or n
Total	654.54	328.65
Mean	1.31	1.31
Minimum	1.10	1.10
Q1	1.22	1.22
Median	1.30	1.29
Q3	1.40	1.40
Maximum	1.65	1.65

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
Database lock date = 31MAR2009

Supplement 25 Efficacy of the vaccine against any RV GE leading to medical intervention from 2 weeks after Dose 2 to database lock, by Cox method-ATP cohort for efficacy

				Person-year rate			VE			
Group	**N**	**n**	**T (year)**	**n/T**	**LL**	**UL**	**%**	**LL**	**UL**	**P-VALUE**
Any RV GE of any G type										
HRV	498	9	649.33	0.014	0.007	0.027	82.70	62.936	91.925	<0.001
Placebo	250	25	314.74	0.079	0.054	0.118	-	-	-	.
Any RV GE of G1 type										
HRV	498	1	654.53	0.002	0.000	0.011	91.67	30.824	98.997	0.021
Placebo	250	6	328.00	0.018	0.008	0.041	-	-	-	.
Any RV GE of Pooled Non G1 type										
HRV	498	8	649.33	0.012	0.006	0.025	79.56	53.312	91.053	<0.001
Placebo	250	19	315.39	0.060	0.038	0.094	-	-	-	.

N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group in the considered efficacy period
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
Database lock date = 31MAR2009

Supplement 26 Efficacy of the vaccine against severe RV GE leading to medical intervention from 2 weeks after Dose 2 up to database lock, by Cox method - ATP cohort for efficacy

				Person-year rate			VE			
Group	**N**	**n**	**T (year)**	**n/T**	**LL**	**UL**	**%**	**LL**	**UL**	**P-VALUE**
Severe RV GE of any type										
HRV	498	1	653.67	0.002	0.000	0.011	95.53	65.395	99.42	0.003
Placebo	250	11	323.62	0.034	0.019	0.061	-	-	-	.
Severe RV GE of G1 type										
HRV	498	0	654.54	0.000	Und.	Und.	100.00	-	100.00	0.995
Placebo	250	4	328.35	0.012	0.005	0.032	-	-	-	.
Severe RV GE of Pooled Non-G1 type										
HRV	498	1	653.67	0.002	0.000	0.011	92.92	42.495	99.129	0.013
Placebo	250	7	323.92	0.022	0.010	0.045	-	-	-	.

N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group in the considered efficacy period.
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
Database lock date = 31MAR2009

Supplement 27 Percentage of subjects reporting any and severe RV GE episodes leading to medical intervention and risk difference of the vaccines from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

Group				Person-year rate			Risk difference		
	N	n	T(Year)	n/ T	LL	UL	RD	LL	UL
Any RV GE									
HRV	498	9	649.33	0.014	0.007	0.027	0.066	0.037	0.104
Placebo	250	25	314.74	0.079	0.054	0.118	.	.	.
Severe RV GE									
HRV	498	1	653.67	0.002	0.00	0.011	0.032	0.015	0.060
Placebo	250	11	323.62	0.034	0.019	0.061	.	.	.

N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(s) in each group
T (Year)= Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Relative difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner
Database lock date = 31MAR2009

Supplement 28 Percentage of subjects reporting any GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 to database - ATP cohort for efficacy

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	191	38.4	34.1	42.8	4.1	-23.4	25.1	0.776
Placebo	250	100	40.0	33.9	46.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

Supplement 29 Percentage of subjects who reported GE, RV GE, severe GE, and severe RV GE episodes leading to medical intervention from Dose 1 up to database lock -Total vaccinated cohort

		HRV N = 508		Placebo N = 257		Total N = 765	
Event	Total number of episodes reported	n	%	n	%	n	%
GE	1	140	27.6	69	26.8	209	27.3
	2	42	8.3	24	9.3	66	8.6
	3	14	2.8	13	5.1	27	3.5
	4	8	1.6	1	0.4	9	1.2
	5	1	0.2	0	0.0	1	0.1
	6	0	0.0	1	0.4	1	0.1
	7	2	0.4	0	0.0	2	0.3
	Any	207	40.7	108	42.0	315	41.2
RV GE	1	9	1.8	26	10.1	35	4.6
	Any	9	1.8	26	10.1	35	4.6
Severe GE	1	45	8.9	27	10.5	72	9.4
	2	1	0.2	5	1.9	6	0.8
	3	1	0.2	0	0.0	1	0.1
	5	1	0.2	0	0.0	1	0.1
	Any	48	9.4	32	12.5	80	10.5
Severe RV GE	1	1	0.2	12	4.7	13	1.7
	Any	1	0.2	12	4.7	13	1.7

N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified number of episode
Any = number (percentage) of subjects reporting at least one specified symptom = sum of the “Total number of episodes reported”
Database Lock date = 31MAR2009

Supplement 30 Number of GE episodes and RV GE episodes leading to medical intervention reported from Dose 1 up to database lock by severity using the 20 point Vesikari scale - Total vaccinated cohort

		HRV		Placebo	
Event	**Severity using the 20 point Vesikari scale**	**n**	**%**	**n**	**%**
GE	**Mild (1-6)**	133	42.0	70	42.2
	Moderate (7-10)	129	40.7	59	35.5
	Severe (≥11)	55	17.4	37	22.3
	Any	317	100	166	100
RV GE	**Mild (1-6)**	6	66.7	6	23.1
	Moderate (7-10)	2	22.2	8	30.8
	Severe (≥11)	1	11.1	12	46.2
	Any	9	100	26	100

n (%) = Number (percentage) of specified events reported in each group, by severity using the 20 point Vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy follow-up period
Database Lock date = 31MAR2009

Supplement 31 Percentage of subjects with RV GE episodes leading to medical intervention reported from Dose 1 up to database lock, by G type and P type - Total vaccinated cohort

	HRV N = 508		Placebo N = 257		Total N = 765	
Serotype	**n**	**%**	**n**	**%**	**n**	**%**
Any	9	1.8	26	10.1	35	4.6
G1 wild type	1	0.2	6	2.3	7	0.9
G2	1	0.2	1	0.4	2	0.3
G3	3	0.6	12	4.7	15	2.0
G4	1	0.2	1	0.4	2	0.3
G9	3	0.6	6	2.3	9	1.2
P4	1	0.2	1	0.4	2	0.3
P8 wild type	8	1.6	25	9.7	33	4.3

N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified serotype in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the serotype
Database Lock date = 31MAR2009

Supplement 32 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from Dose 1 up to database lock, by G type and P type - Total vaccinated cohort

	HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	Value or n	%	Value or n	%	Value or n	%
Any	1	0.2	12	4.7	13	1.7
G1 wild type	0	0.0	4	1.6	4	0.5
G3	0	0.0	5	1.9	5	0.7
G9	1	0.2	3	1.2	4	0.5
P8 wild type	1	0.2	12	4.7	13	1.7

N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified serotype in each group
Any = number of subjects reporting at least one severe rotavirus gastroenteritis episodes, whatever is the serotype
Database Lock date = 31MAR2009

Supplement 33 Duration (in years) of efficacy follow-up period from Dose 1 up to database lock - Total vaccinated cohort

Duration (years) of follow-up period	HRV N = 508	Placebo N = 257
	Value or n	Value or n
Total	736.94	372.99
Mean	1.45	1.45
Minimum	1.25	1.26
Q1	1.35	1.35
Median	1.43	1.43
Q3	1.53	1.54
Maximum	1.78	1.78

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
Database lock date = 31MAR2009

Supplement 34 Percentage of subjects reporting any RV GE episode leading to medical intervention and efficacy of the vaccine from Dose 1 to database lock - Total vaccinated cohort

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	508	9	1.8	0.8	3.3	82.5	61.4	92.8	<0.001
Placebo	257	26	10.1	6.7	14.5	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

Supplement 35 Percentage of subjects reporting any RV GE episode leading to medical intervention and efficacy of the vaccine from Dose 1 up to database lock, by RV types - Total vaccinated cohort

				n/N			VE			
Serotype	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
G1WT	**HRV**	508	1	0.2	0.0	1.1	91.6	30.5	99.8	0.014
	Placebo	257	6	2.3	0.9	5.0	-	-	-	-
G2	**HRV**	508	1	0.2	0.0	1.1	49.4	-3871.2	99.4	1.000
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
G3	**HRV**	508	3	0.6	0.1	1.7	87.4	53.1	97.7	<0.001
	Placebo	257	12	4.7	2.4	8.0	-	-	-	-
G4	**HRV**	508	1	0.2	0.0	1.1	49.4	-3871.2	99.4	1.000
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
G9	**HRV**	508	3	0.6	0.1	1.7	74.7	-18.4	95.9	0.088
	Placebo	257	6	2.3	0.9	5.0	-	-	-	-
P4	**HRV**	508	1	0.2	0.0	1.1	49.4	-3871.2	99.4	1.000
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
P8	**HRV**	508	8	1.6	0.7	3.1	83.8	63.0	93.7	<0.001
	Placebo	257	25	9.7	6.4	14.0	-	-	-	-
Pooled	**HRV**	508	8	1.6	0.7	3.1	79.8	52.0	92.3	<0.001
Non-G1	**Placebo**	257	20	7.8	4.8	11.8	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Database lock date = 31MAR2009

Supplement 36 Percentage of subjects reporting severe RV GE episode leading to medical intervention and efficacy of the vaccine from Dose 1 to database lock - Total vaccinated cohort

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	508	1	0.2	0.0	1.1	95.8	71.5	99.9	<0.001
Placebo	257	12	4.7	2.4	8.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

Supplement 37 Percentage of subjects reporting severe RV GE episode leading to medical intervention and efficacy of the vaccine from Dose 1 up to database lock, by RV types - Total vaccinated cohort

				n/N			VE			
Serotype	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
G1 WT	**HRV**	508	0	0.0	0.0	0.7	100.0	23.4	100.0	0.025
	Placebo	257	4	1.6	0.4	3.9	-	-	-	-
G3	**HRV**	508	0	0.0	0.0	0.7	100.0	44.8	100.0	0.009
	Placebo	257	5	1.9	0.6	4.5	-	-	-	-
G9	**HRV**	508	1	0.2	0.0	1.1	83.1	-110.0	99.7	0.227
	Placebo	257	3	1.2	0.2	3.4	-	-	-	-
P8	**HRV**	508	1	0.2	0.0	1.1	95.8	71.5	99.9	<0.001
	Placebo	257	12	4.7	2.4	8.0	-	-	-	-
Pooled	**HRV**	508	1	0.2	0.0	1.1	93.7	52.8	99.9	0.002
Non-G1	**Placebo**	257	8	3.1	1.4	6.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
Database lock date = 31MAR2009

Supplement 38 Efficacy of the vaccine against any RV GE leading to medical intervention from Dose 1 up to database lock, by Cox method- Total vaccinated cohort

				Person-year rate			VE			
Group	**N**	**n**	**T (year)**	**n/T**	**LL**	**UL**	**%**	**LL**	**UL**	**P-VALUE**
Any RV GE of any G type										
HRV	508	9	731.73	0.012	0.006	0.024	83.27	64.297	92.161	<0.001
Placebo	257	26	358.12	0.073	0.049	0.107	-	-	-	.
Any RV GE of G1 type										
HRV	508	1	736.94	0.001	0.000	0.010	91.64	30.524	98.993	0.022
Placebo	257	6	372.35	0.016	0.007	0.036	-	-	-	.
Any RV GE of Pooled Non G1 type										
HRV	508	8	731.73	0.011	0.005	0.022	80.48	55.688	91.404	<0.001
Placebo	257	20	358.77	0.056	0.036	0.086	-	-	-	.

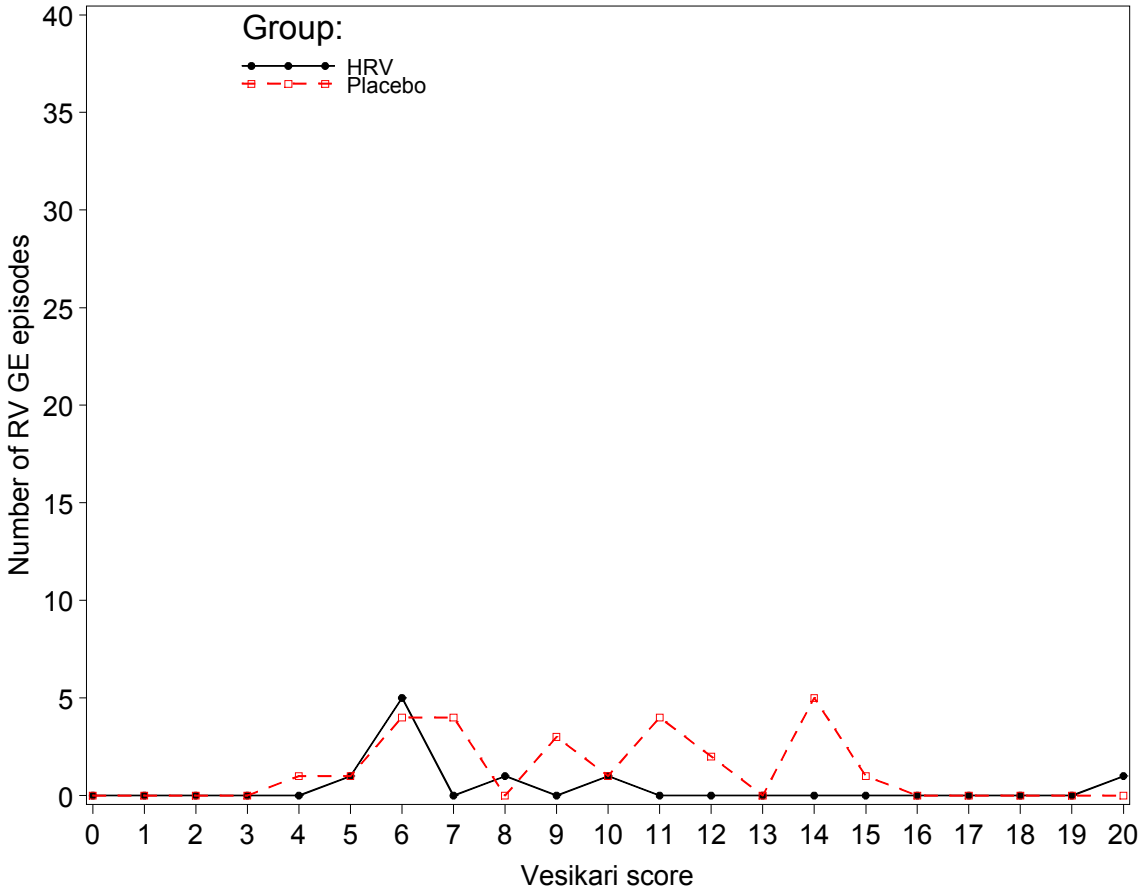
N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group in the considered efficacy period
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
Database lock date = 31MAR2009

Supplement 39 Percentage of subjects reporting any and severe RV GE episodes leading to medical intervention and risk difference of the vaccines from Dose 1 up to database lock - Total vaccinated cohort

Group				Person-year rate			Risk difference		
	N	n	T(Year)	n/ T	LL	UL	RD	LL	UL
Any RV GE									
HRV	508	9	731.73	0.012	0.006	0.024	0.060	0.035	0.095
Placebo	257	26	358.12	0.073	0.049	0.107	.	.	.
Severe RV GE									
HRV	508	1	736.08	0.001	0	0.01	0.031	0.015	0.056
Placebo	257	12	367	0.033	0.019	0.058	.	.	.

N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(S) in each group
T (Year)= Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Relative difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner
Database lock date = 31MAR2009

Supplement 40 Distribution of Vesikari score for RV GE episodes leading to medical intervention reported from dose 1 up to database lock – Total vaccinated cohort



Supplement 41 Compliance in returning symptom sheets (Total vaccinated cohort)

Dose	Group	Number of doses	Doses NOT according to protocol	Number of general SS	Compliance % general SS
1	HRV	508	0	508	100
	Placebo	257	0	257	100
2	HRV	499	0	499	100
	Placebo	250	0	250	100
Total	HRV	1007	0	1007	100
	Placebo	507	0	507	100

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100

Supplement 42 Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)

		Any symptoms				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV	508	24	4.7	3.1	6.9
	Placebo	257	7	2.7	1.1	5.5
Dose 2	HRV	499	18	3.6	2.2	5.6
	Placebo	250	3	1.2	0.2	3.5
Overall/dose	HRV	1007	42	4.2	3.0	5.6
	Placebo	507	10	2.0	0.9	3.6
Overall/subject	HRV	508	40	7.9	5.7	10.6
	Placebo	257	9	3.5	1.6	6.5

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n (%)= number (percentage) of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 43 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as causally related to vaccination during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)

		Any symptoms				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV	508	33	6.5	4.5	9.0
	Placebo	257	13	5.1	2.7	8.5
Dose 2	HRV	499	41	8.2	6.0	11.0
	Placebo	250	14	5.6	3.1	9.2
Overall/dose	HRV	1007	74	7.3	5.8	9.1
	Placebo	507	27	5.3	3.5	7.7
Overall/subject	HRV	508	62	12.2	9.5	15.4
	Placebo	257	24	9.3	6.1	13.6

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n (%)= number (percentage) of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 44 Percentage of doses and subjects reporting each solicited general symptom including those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period, for each dose (Total vaccinated cohort)

		HRV					Placebo				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose											
Cough/runny nose	All	1007	237	23.5	20.9	26.3	507	113	22.3	18.7	26.2
	Grade 3	1007	2	0.2	0.0	0.7	507	1	0.2	0.0	1.1
	Related	1007	20	2.0	1.2	3.1	507	2	0.4	0.0	1.4
Diarrhoea	All	1007	49	4.9	3.6	6.4	507	16	3.2	1.8	5.1
	Grade 3	1007	11	1.1	0.5	1.9	507	2	0.4	0.0	1.4
	Related	1007	20	2.0	1.2	3.1	507	8	1.6	0.7	3.1
Fever	All	1007	71	7.1	5.5	8.8	507	24	4.7	3.1	7.0
	Grade 3	1007	3	0.3	0.1	0.9	507	0	0.0	0.0	0.7
	Related	1007	7	0.7	0.3	1.4	507	0	0.0	0.0	0.7
Irritability	All	1007	357	35.5	32.5	38.5	507	170	33.5	29.4	37.8
	Grade 3	1007	15	1.5	0.8	2.4	507	4	0.8	0.2	2.0
	Related	1007	43	4.3	3.1	5.7	507	19	3.7	2.3	5.8
Loss of appetite	All	1007	95	9.4	7.7	11.4	507	38	7.5	5.4	10.1
	Grade 3	1007	1	0.1	0.0	0.6	507	0	0.0	0.0	0.7
	Related	1007	10	1.0	0.5	1.8	507	2	0.4	0.0	1.4
Vomiting	All	1007	90	8.9	7.2	10.9	507	42	8.3	6.0	11.0
	Grade 3	1007	14	1.4	0.8	2.3	507	3	0.6	0.1	1.7
	Related	1007	7	0.7	0.3	1.4	507	2	0.4	0.0	1.4
Overall/subject											
Cough/runny nose	All	508	184	36.2	32.0	40.6	257	92	35.8	29.9	42.0
	Grade 3	508	2	0.4	0.0	1.4	257	1	0.4	0.0	2.1
	Related	508	17	3.3	2.0	5.3	257	2	0.8	0.1	2.8
Diarrhoea	All	508	43	8.5	6.2	11.2	257	14	5.4	3.0	9.0
	Grade 3	508	10	2.0	0.9	3.6	257	2	0.8	0.1	2.8
	Related	508	18	3.5	2.1	5.5	257	7	2.7	1.1	5.5
Fever	All	508	62	12.2	9.5	15.4	257	22	8.6	5.4	12.7
	Grade 3	508	3	0.6	0.1	1.7	257	0	0.0	0.0	1.4
	Related	508	7	1.4	0.6	2.8	257	0	0.0	0.0	1.4
Irritability	All	508	261	51.4	46.9	55.8	257	125	48.6	42.4	54.9
	Grade 3	508	15	3.0	1.7	4.8	257	4	1.6	0.4	3.9
	Related	508	37	7.3	5.2	9.9	257	17	6.6	3.9	10.4
Loss of appetite	All	508	81	15.9	12.9	19.4	257	33	12.8	9.0	17.6
	Grade 3	508	1	0.2	0.0	1.1	257	0	0.0	0.0	1.4
	Related	508	9	1.8	0.8	3.3	257	2	0.8	0.1	2.8
Vomiting	All	508	74	14.6	11.6	17.9	257	36	14.0	10.0	18.9
	Grade 3	508	13	2.6	1.4	4.3	257	2	0.8	0.1	2.8
	Related	508	7	1.4	0.6	2.8	257	2	0.8	0.1	2.8

For overall/subject:
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once the symptom
For Overall/dose:
N= number of administered doses
n (%)= number (percentage) of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Supplement 45 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

	HRV N = 1007				Placebo N = 507			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	354	35.2	32.2	38.2	181	35.7	31.5	40.0
Blood and lymphatic system disorders (10005329)	*1*				*1*			
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
Ear and labyrinth disorders (10013993)	4	0.4	0.1	1.0	1	0.2	0.0	1.1
Eye disorders (10015919)	30	3.0	2.0	4.2	13	2.6	1.4	4.3
Gastrointestinal disorders (10017947)	41	4.1	2.9	5.5	24	4.7	3.1	7.0
General disorders and administration site conditions (10018065)	9	0.9	0.4	1.7	8	1.6	0.7	3.1
Hepatobiliary disorders (10019805)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
Infections and infestations (10021881)	128	12.7	10.7	14.9	66	13.0	10.2	16.3
Injury, poisoning and procedural complications (10022117)	4	0.4	0.1	1.0	6	1.2	0.4	2.6
Metabolism and nutrition disorders (10027433)	*1*				*1*			
Musculoskeletal and connective tissue disorders (10028395)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
Nervous system disorders (10029205)	*2*				*2*			
Psychiatric disorders (10037175)	*1*				*1*			
Respiratory, thoracic and mediastinal disorders (10038738)	74	7.3	5.8	9.1	49	9.7	7.2	12.6
Skin and subcutaneous tissue disorders (10040785)	147	14.6	12.5	16.9	60	11.8	9.2	15.0

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of administered doses
n (%) = number (percentage) of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
n = n cases reported in one group and none in the other group. Those cases remain blinded as study is ongoing.

Supplement 46 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

	HRV N = 1007				Placebo N = 507			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	7	0.7	0.3	1.4	2	0.4	0.0	1.4
Gastrointestinal disorders (10017947)	7	0.7	0.3	1.4	2	0.4	0.0	1.4

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of administered doses
n (%) = number (percentage) of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 47 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

	HRV N = 1007				Placebo N = 507			
			95% CI				95% CI	
Primary System Organ Class (CODE)	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom	14	1.4	0.8	2.3	9	1.8	0.8	3.3
Gastrointestinal disorders (10017947)	*2*				*2*			
Hepatobiliary disorders (10019805)	*1*				*1*			
Infections and infestations (10021881)	8	0.8	0.3	1.6	6	1.2	0.4	2.6
Respiratory, thoracic and mediastinal disorders (10038738)	1	0.1	0.0	0.6	2	0.4	0.0	1.4
Skin and subcutaneous tissue disorders (10040785)	2	0.2	0.0	0.7	1	0.2	0.0	1.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
N = number of administered doses
n (%) = number (percentage) of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
n = n cases reported in one group and none in the other group. Those cases remain blinded as study is ongoing.

Supplement 48 Listings of SAEs (Total vaccinated cohort)

Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Intensity	Causality	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 49 Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after each vaccination by type (Total vaccinated cohort)

	HRV					Placebo				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1										
Any	508	87	17.1	14.0	20.7	257	32	12.5	8.7	17.1
Any antipyretic	508	8	1.6	0.7	3.1	257	7	2.7	1.1	5.5
Prophylactic antipyretic	508	0	0.0	0.0	0.7	257	0	0.0	0.0	1.4
Any antibiotic	508	22	4.3	2.7	6.5	257	3	1.2	0.2	3.4
Dose 2										
Any	499	70	14.0	11.1	17.4	250	41	16.4	12.0	21.6
Any antipyretic	499	7	1.4	0.6	2.9	250	5	2.0	0.7	4.6
Prophylactic antipyretic	499	0	0.0	0.0	0.7	250	0	0.0	0.0	1.5
Any antibiotic	499	14	2.8	1.5	4.7	250	7	2.8	1.1	5.7
Overall/dose										
Any	1007	157	15.6	13.4	18.0	507	73	14.4	11.5	17.8
Any antipyretic	1007	15	1.5	0.8	2.4	507	12	2.4	1.2	4.1
Prophylactic antipyretic	1007	0	0.0	0.0	0.4	507	0	0.0	0.0	0.7
Any antibiotic	1007	36	3.6	2.5	4.9	507	10	2.0	0.9	3.6
Overall/subject										
Any	508	142	28.0	24.1	32.1	257	64	24.9	19.7	30.7
Any antipyretic	508	14	2.8	1.5	4.6	257	11	4.3	2.2	7.5
Prophylactic antipyretic	508	0	0.0	0.0	0.7	257	0	0.0	0.0	1.4
Any antibiotic	508	36	7.1	5.0	9.7	257	10	3.9	1.9	7.0

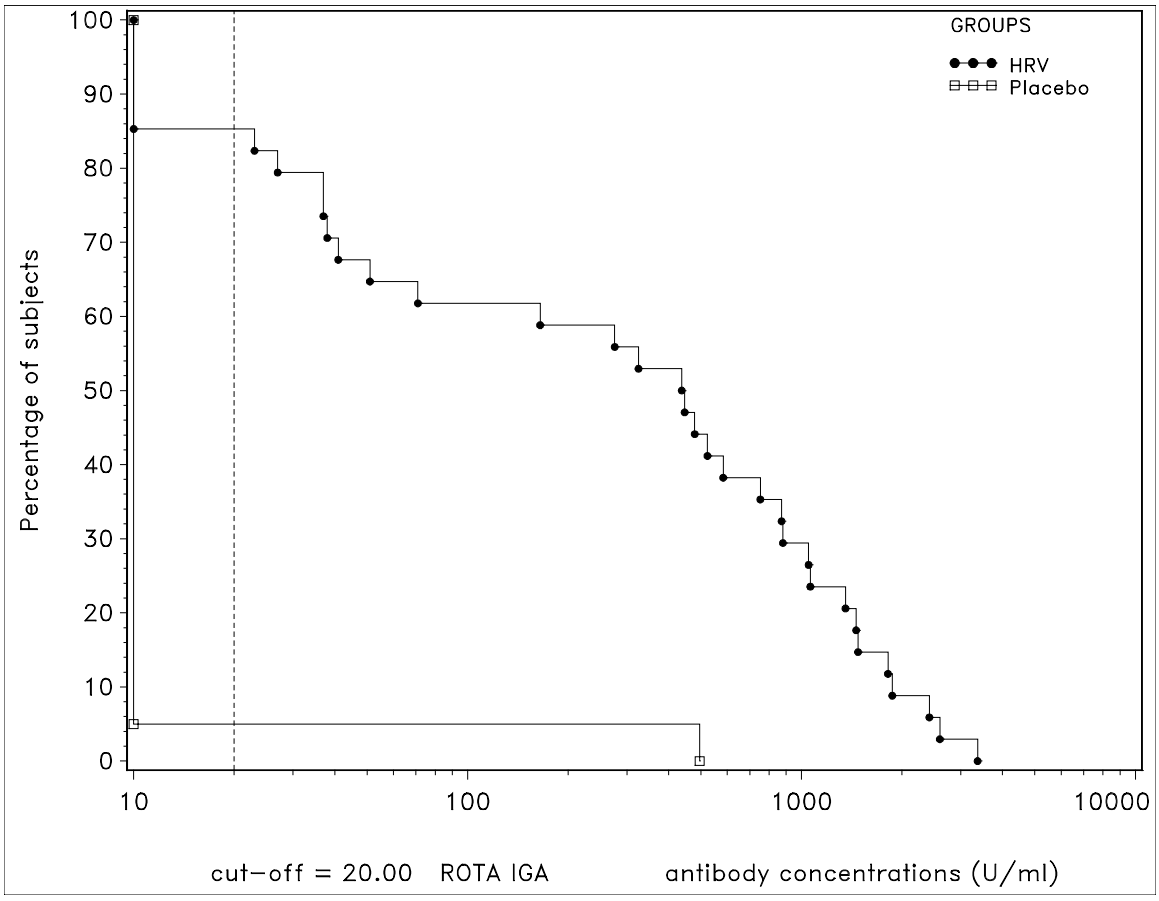
For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects who started to take the specified concomitant medication at least once during the mentioned period
For overall/dose:
N= number of administered doses
n (%)= number (percentage) of doses after which the specified concomitant medication was started at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Supplement 50 Number and percentage of doses and of subjects who took at least one concomitant medication during the study period (from Dose 1 till database lock) by type (Total vaccinated cohort)

	HRV					Placebo				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1										
Any	508	165	32.5	28.4	36.7	257	70	27.2	21.9	33.1
Any antipyretic	508	16	3.1	1.8	5.1	257	13	5.1	2.7	8.5
Prophylactic antipyretic	508	0	0.0	0.0	0.7	257	0	0.0	0.0	1.4
Any antibiotic	508	59	11.6	9.0	14.7	257	22	8.6	5.4	12.7
Dose 2										
Any	499	217	43.5	39.1	48.0	250	122	48.8	42.5	55.2
Any antipyretic	499	32	6.4	4.4	8.9	250	21	8.4	5.3	12.6
Prophylactic antipyretic	499	0	0.0	0.0	0.7	250	0	0.0	0.0	1.5
Any antibiotic	499	105	21.0	17.5	24.9	250	51	20.4	15.6	25.9
Overall/dose										
Any	1007	382	37.9	34.9	41.0	507	192	37.9	33.6	42.3
Any antipyretic	1007	48	4.8	3.5	6.3	507	34	6.7	4.7	9.2
Prophylactic antipyretic	1007	0	0.0	0.0	0.4	507	0	0.0	0.0	0.7
Any antibiotic	1007	164	16.3	14.1	18.7	507	73	14.4	11.5	17.8
Overall/subject										
Any	508	300	59.1	54.6	63.4	257	155	60.3	54.0	66.3
Any antipyretic	508	43	8.5	6.2	11.2	257	32	12.5	8.7	17.1
Prophylactic antipyretic	508	0	0.0	0.0	0.7	257	0	0.0	0.0	1.4
Any antibiotic	508	152	29.9	26.0	34.1	257	65	25.3	20.1	31.1

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n (%)= number (percentage) of subjects who started to take the specified concomitant medication at least once during the mentioned period
For overall/dose:
N= number of administered doses
n (%)= number (percentage) of doses after which the specified concomitant medication was started at least once during the mentioned period
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Database lock date = 31 Mar 2009

Supplement 51 Reverse Cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 from a subset of subjects - ATP cohort for immunogenicity



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Director, Rotavirus vaccines
Global Clinical Research and Development

14. SERIOUS ADVERSE EVENTS

14.1. SAE Summary Table

Listings of SAEs (Total Vaccinated Cohort)

14.2. CIOMS

As the study is still ongoing, the blinding will be maintained for the whole study period. CIOMS will be available at the time of the annex report.

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
Randomization list (patient identification and treatment assigned).	16.1.7
Audit certificates (if available).	16.1.8
Documentation of statistical methods	16.1.9
Documentation of inter-laboratory standardization methods and quality assurance procedures, if used.	16.1.10
Publications based on the study.	16.1.11
Important publications referenced in the report	16.1.12
Individual listings	16.2
Case report forms (CRFs /eCRFs) CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events	16.3 16.3.1

Sponsor Information Sheet

eTrack study number(s) and Abbreviated Title(s)	107625 (Rota-056)
Date of document	09 October 2009
Version of document	Version 1
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

1. Country

Japan

2. Co-ordinating Investigator/ Leiter der Klinishen Prüfung / Principal Investigators

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[redacted]

[redacted]

[redacted]s)

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[redacted]

[redacted]

[redacted]

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3. Medical Monitor

Not applicable

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6. Study Contact for Emergency Code Break

GSK Biologicals Clinical Safety Physician
(Study Contact for Emergency Code Break)
Tel: [redacted]
Fax: [redacted] or [redacted]
Mobile phones for 7/7 day availability:
[redacted] (Head Safety Evaluation and Risk Management Pediatric)
Back-up mobile phone contact:
[redacted]

7. Study Centres

This study was conducted at 20 centres in Japan.

Protocol and Protocol Amendments

Sponsor:
GSK Building
6-15, Sendagaya 4-chome
Shibuya-ku, Tokyo 151-8566
Japan

Study vaccine number	444563
Study vaccine	Lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	107625 (Rota-056)
Date of approval	Final: 30 March 2007
Amendment 1	Final: 07 May 2007
Title	Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Rotavirus Vaccine • [redacted] Central Study Co-ordinator • [redacted] Central Study Co-ordinator • [redacted] Statistician • [redacted] Manager, Clinical Development
Sponsor signatory:	[redacted] Director, Worldwide Clinical Development, Rotavirus vaccine, GSK Biologicals. [redacted] Deputy Director, Clinical Development, GlaxoSmithKline K.K.

GSK Biologicals' Protocol DS V 12.4

Synopsis

Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Indication/Study population	Primary immunisation of healthy infants against rotavirus disease/illness.
Rationale	GSK Biologicals' rotavirus vaccine is a live attenuated vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. The formulation consisting of a lyophilised HRV vaccine to be reconstituted with a suspension of calcium carbonate has been tested extensively in Phase I, II and III trials in a global development program and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants. This registration study is undertaken to provide the Regulatory Authorities in Japan with immunogenicity, efficacy, safety and reactogenicity data for the lyophilised formulation of GSK Biologicals' HRV vaccine when used in Japanese infants aged approximately 2 months at the time of the first dose. There will be an efficacy follow-up up to the time the infants are approximately two years of age.
Objectives	**Primary** • To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period. **Secondary** **Efficacy** • To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period. • To assess the efficacy of two doses of the lyophilised

formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.
- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity [in the immunogenicity subset (N = 60)]

- To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

Study design

- Experimental design: Phase III, randomised, double-blind, placebo-controlled, multicentre study in Japan with two parallel groups.
- Treatment allocation: Randomised (2:1 ratio).
- Blinding: Double-blind. Blinding will be maintained till the end of the study, i.e. Visit 5.

- Treatment Groups:
  - Group HRV lyophilised vaccine (N = 510)
  - Group Placebo (N = 255)
- Vaccination schedule: Vaccination according to 0, 1 month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks (42–104 days) at the time of the first dose.
- Control: Placebo.
- Routine childhood vaccination according to local practice can be administered concurrently with the study vaccinations as recommended in Japan. All vaccines administered from birth up to Visit 3 must be documented in the electronic case report form (eCRF).
- Eight day (Day 0 – Day 7) follow-up period for solicited symptoms (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) after any dose of HRV vaccine/Placebo using diary cards. Unsolicited symptoms will be followed up for a period of 31 days (Day 0 – Day 30).
- During the entire study period (from Dose 1 up to Visit 5 [two years of age]), active follow-up for occurrence of GE episodes (diarrhoea) leading to medical intervention via telephone contact or other means (at least every two weeks).
- For each GE episode leading to medical intervention occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after symptoms begin but preferably not later than 7 days after the onset of GE symptoms.
- Recording of SAEs throughout the study period.
- Blood samples (1 ml of whole blood to provide 0.4 ml of serum) will be drawn from subjects in the immunogenicity subset (N = 60) at Day 0 (i.e. Visit 1) and one month post Dose 2 (Month 2 i.e. Visit 3) to measure anti-rotavirus IgA antibody concentrations.
- Type of study: Self-contained.
- Data collection: Remote Data Entry (RDE).
- Five scheduled visits per subject: at Months 0, 1, 2 and

one and two years of age.

- Duration of the study: The intended duration of the study, per subject will be till the subject is two years of age.
- Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

Number of subjects Target enrolment will be 765 subjects (510 subjects in HRV lyophilised vaccine group and 255 subjects in Placebo Group).

Primary endpoint

- Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- 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/Placebo.

- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Immunogenicity (in the immunogenicity subset N = 60)

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 3.

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TABLES

APPENDICES

List of Abbreviations

AE	Adverse event
AR	Attack rate
ATP	According-to-protocol
$CCID_{50}$	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
CTN	Clinical trial notification
DMEM	Dulbecco's Modified Eagle Medium
DTPa	Combined diphtheria, tetanus- acellular cell pertussis
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
eTrack	GSK tracking tool
Ffu	Foci Forming Units
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
HRV	Human Rotavirus
IB	Investigator Brochure
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
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
PCR	Polymerase Chain Reaction
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBIR	Internet Randomisation tool
SOP	Standard Operating Procedure
UNICEF	United Nations Children's Fund
VE	Vaccine Efficacy
WHO	World Health Organisation

Glossary of Terms

Adverse event (AE):	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. When the subject, 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. 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 the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Diarrhoea:	Passage of three or more looser than normal stools within a day.
Efficacy follow-up period:	Period starting from two weeks after Dose 2 of HRV vaccine or placebo and ending either when 28 RV GE cases leading to medical intervention and caused by the circulating wild-type RV strains is accumulated or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all

	subjects reach two years of age, a final report will be present efficacy/safety/immunogenicity data up to time 28 RV GE episodes is reached and an annex report will present the efficacy/safety data up to two years of age.
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).
Gastroenteritis:	Diarrhoea with or without vomiting.
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 intervention:	Defined as medical doctor visit, an emergency room visit or hospitalisation
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 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.
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.

Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection
RV GE for primary efficacy analysis:	An episode of any severity GE leading to a medical intervention occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.
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:	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 number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subject:	Term used throughout the protocol 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.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

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 randomisation or treatment allocation.
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. INTRODUCTION

Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) among children worldwide. Review of epidemiological data estimated that, world-wide, RV causes approximately 138 -140 million cases of diarrhoea annually accounting for 20% of outpatient or clinic visits for diarrhoea, 26% of hospitalisations for diarrhoea and an estimated 440,000 deaths in children under 5 years of age per year [Parashar, 2003]. New surveillance data suggest that previous data are an underestimate and the mortality rate is now estimated to be as high as 611,000 (range 454,000 –705,000) annual deaths world-wide [Parashar, 2006]. The majority of these deaths occur in Africa, Indian subcontinent and Latin America. In developed countries, RV infection rarely results in death but RV remains the most common cause of hospitalisation for GE in children and leads to major medical and societal costs.

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 oral live attenuated vaccines receiving the most attention.

To meet this health need, GlaxoSmithKline (GSK) Biologicals has developed an attenuated vaccine which is based on a human rotavirus (HRV) strain designated as RIX4414. The vaccine strain RIX4414 was derived from the parent 89-12 HRV strain belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old child with a mild RV diarrhoea in December 1988. A candidate vaccine based on the 89-12 HRV strain at passage 33 in African Green Monkey Kidney cells was shown to be safe, immunogenic and efficacious against RV GE over two consecutive RV seasons in infants [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002]. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilised HRV vaccine containing RIX4414, a cloned passage 43 derivative from 89-12, for oral administration after reconstitution with a separately supplied liquid calcium carbonate buffer.

1.1. Background

GSK Biologicals' HRV vaccine (Rotarix) is currently licensed in a total of 89 countries in Latin America, Asia, Middle-East, Africa and the European Union.

GSK Biologicals' HRV vaccine was tested in Phase I studies conducted in adults, previously infected children (1-3 years old), followed by Phase II and Phase III studies among infants in Asia, Africa, Europe, Latin America and North America. In all studies, the adverse reaction profile in infants receiving HRV vaccine was similar to infants receiving Placebo. A large safety trial conducted in Latin America and Finland where 63,225 subjects were enrolled gave evidence of no increased risk of intussusception (IS) in the HRV vaccine Group when compared with the Placebo Group. The HRV vaccine was highly efficacious in protecting infants against RV GE.

The protective efficacy of the HRV vaccine against any or severe RV GE, as well as against hospitalisation for RV GE was demonstrated in phase II studies in Finland [Vesikari, 2004] and Latin America (Brazil, Mexico and Venezuela) [Salinas, 2005].

In Finland (Study Rota-004) [Vesikari, 2004], two doses of HRV 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.

In Latin America (Brazil, Mexico and Venezuela) (Study Rota-006) [Salinas, 2005], the efficacy of the HRV vaccine in preventing RV GE was demonstrated in a setting with different circulating serotypes (G1 and non-G1 RV types). Two doses of the HRV vaccine at three virus concentrations ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu) were 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-HBV] and Hib). For the first year efficacy follow-up, the protective efficacy of the HRV vaccine (pooled HRV vaccine Groups) was 61.4% (95% CI: 42.3%; 74.1%) against any RV diarrhoea, 74.1% (95% CI: 55.8%; 85.0%) against severe RV diarrhoea (an episode with a score ≥ 11 on the 20-point Vesikari scale [Ruuska, 1990]) and 79.0% (95% CI: 48.0%; 92.0%) against hospitalised RV diarrhoea. The vaccine efficacy against severe RV GE was 74.7% (95% CI: 37.7%; 90.1%) over two consecutive efficacy follow-up periods.

A large phase III multinational trial (Rota-023) involving 63,225 infants was undertaken in 11 countries in Latin America and in Finland with a co-primary objective of assessing the safety of the HRV vaccine in terms of occurrence of definite IS [Ruiz-Palacios, 2006]. The primary safety evaluation was based on occurrence of definite IS during 31 days (Day 0 to Day 30) after each vaccine dose. 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. The overall SAE profile of the HRV vaccine was similar to the Placebo. The SAE profile appeared to be in favour of the HRV vaccine with respect to preventing GE-related SAEs.

Study Rota-023 is 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. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV strains during the period starting from completion of the immunisation (2 weeks post Dose 2) until one year of age was 84.7% (95% CI: 71.7%; 92.4%) (primary efficacy endpoint). 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%). A subset of children was followed up until 24 months of age. Vaccine efficacy against severe RV GE was 79.0% (95% CI: 66.4%; 87.4%) during the second year and 80.5% (95% CI: 71.3%; 87.1%) during the

entire two year follow-up. Efficacy against G1 and non-G1 RV types was consistent during each follow-up period. The results from this study confirm that this human attenuated G1P[8] HRV vaccine elicits cross-protection, and provide evidence that the HRV vaccine effectively protects vaccinated children against the commonly circulating RV types during the first two years of life. Among the subjects followed until one year of age and until two years of age, there was no increased risk of definite IS respectively diagnosed from Dose 1 up to one year of age and from Dose 1 up to two years of age in the HRV vaccine Group versus Placebo.

A phase III study conducted in six European countries (Rota-036) evaluated two doses of the HRV vaccine when co-administered with routine infant vaccinations: Infanrix Hexa (combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated polio and *Haemophilus influenzae* type b vaccine), Infanrix Polio Hib (combined diphtheria and tetanus toxoids, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine), Prevnar (7-valent pneumococcal polysaccharide conjugate vaccine) and Meningitec (meningococcal group C conjugate vaccine). This study has confirmed the efficacy of HRV vaccine against RV GE hospitalisations, any and severe RV GE due to G1 and non-G1 RV and the important reduction of severe GE of any cause. The first efficacy follow-up period started from two weeks after Dose 2 and ended June –July 2005. A total of 3874 subjects were part of the 1st year according-to-protocol (ATP) cohort for efficacy. Vaccine efficacy was 87.1% (95% CI: 79.6%; 92.1%) against any episodes of RV GE and 95.8% (95% CI: 89.6%; 98.7%) against severe RV GE episodes. For increasing disease severity with Vesikari scores between 11 and 20, VE was increasingly higher, reaching 100% against more severe RV GE (Vesikari score ≥ 17 points). VE against hospitalisation for RV GE was 100% (95% CI: 81.8%; 100%) and against RV GE episodes requiring medical attention was 91.8% (95% CI: 84.0%; 96.3%). The HRV vaccine was significantly protective against any and severe RV GE caused by G1, G3, G4 and G9 RV strains. Protective trend was observed against G2 RV type that does not share any of the outer or inner capsid antigens of the HRV vaccine.

Study Rota-036 also provided key co-administration data by evaluating the co-administration of HRV vaccine with currently used childhood vaccinations given according to the primary vaccination schedules in each participating country. Co-administration of HRV vaccine with routinely used Infanrix Hexa, Infanrix Polio Hib, Prevnar 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 Geometric Mean antibody Concentration/Titre (GMCs/GMTs) for antibodies to diphtheria, tetanus, pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), hepatitis B surface antigen (HBs), poliovirus serotypes 1, 2 and 3, and polyribosyl ribitol phosphate (PRP) were similar between the HRV vaccine and Placebo Groups after three doses of childhood vaccinations. In France and Germany, Post Dose 3 response to each of the seven *Streptococcus pneumoniae* serotypes, 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.

Please refer to the latest edition of the Investigator Brochure (edition 7 or later) for a review of the pre-clinical and clinical studies of GSK Biologicals' HRV vaccine.

1.2. Rationale for the study

GSK Biologicals' rotavirus vaccine is a live attenuated vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. The formulation consisting of a lyophilised HRV vaccine to be reconstituted with a suspension of calcium carbonate has been tested extensively in Phase I, II and III trials in a global development program and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.

This registration study is being undertaken to provide the Regulatory Authorities in Japan with immunogenicity, efficacy, safety and reactogenicity data for the lyophilised formulation of GSK Biologicals' HRV vaccine when used in Japanese infants aged approximately 2 months at the time of the first dose. There will be an efficacy follow-up up to the time that the infants are approximately two years of age.

2. OBJECTIVES

2.1. Primary objective

- To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

Efficacy

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

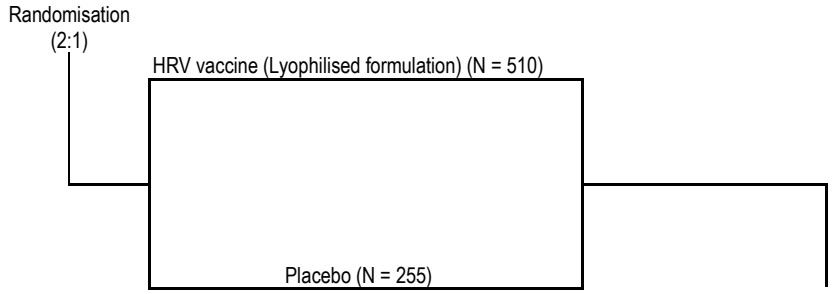
- To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.
- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity [in the immunogenicity subset (N = 60)]

- To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW



	Vaccination Visits			Safety and efficacy follow-up Visits	
	Visit 1	Visit 2	Visit 3	Visit 4#	Visit 5#
	Dose 1	Dose 2			
	Day 0	Month 1	Month 2		
Age:	6 – 14 weeks			1 year	2 years
	Blood sampling*		Blood sampling*		

N: Number of subjects planned to be enrolled.
HRV: Human rotavirus
*: Blood sampling in the immunogenicity subset (N = 60)
#: Safety and efficacy follow-up visits.

- Experimental design: Phase III, randomised, double-blind, placebo-controlled, multicentre study in Japan with two parallel groups.
- Treatment allocation: Randomised (2:1 ratio).
- Blinding: Double-blind. Blinding will be maintained till the end of the study, i.e. Visit 5.
- Treatment Groups:
  - Group HRV lyophilised vaccine (N = 510)
  - Group Placebo (N = 255)
- Vaccination schedule: Vaccination according to 0, 1 month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks (42–104 days) at the time of the first dose.
- Control: Placebo.
- Routine childhood vaccination according to local practice can be administered concurrently with the study vaccinations as recommended in Japan. All vaccines administered from birth up to Visit 3 must be documented in the electronic case report form (eCRF).
- Eight day (Day 0 – Day 7) follow-up period for solicited symptoms (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) after any dose of HRV vaccine/Placebo using diary cards. Unsolicited symptoms will be followed up for a period of 31 days (Day 0 – Day 30).
- During the entire study period (from Dose 1 up to Visit 5 [two years of age]), active follow-up for occurrence of GE episodes (diarrhoea) leading to medical intervention via telephone contact or other means (at least every two weeks).
- For each GE episode leading to medical intervention occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after symptoms begin but preferably not later than 7 days after the onset of GE symptoms.
- Recording of SAEs throughout the study period.
- Blood samples (1 ml of whole blood to provide 0.4 ml of serum) will be drawn from subjects in the immunogenicity subset (N = 60) at Day 0 (i.e. Visit 1) and one month post Dose 2 (Month 2 i.e. Visit 3) to measure anti-rotavirus IgA antibody concentrations.
- Type of study: Self-contained.
- Data collection: Remote Data Entry (RDE).
- Five scheduled visits per subject: at Months 0, 1, 2 and one and two years of age.
- Duration of the study: The intended duration of the study, per subject will be till the subject is two years of age (refer to Appendix C for recruitment details).

- Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

4. STUDY COHORT

4.1. Number of subjects/centres

Target enrolment will be 765 subjects (510 subjects in HRV lyophilised vaccine Group and 255 subjects in Placebo Group). All subjects will be enrolled at multiple sites in Japan.

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) should be enrolled in the study.

- A male or female infant 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/guardian of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born between a gestation period of 36 and 42 weeks inclusive.

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 within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- History of use of experimental rotavirus vaccine.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs prior to the first vaccine dose. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)

- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition determined by the investigator.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- A family history of congenital or hereditary immunodeficiency.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.
- 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. Axillary temperature <37.5°C.) Temperature greater than or equal to these cut-offs warrants deferral of the vaccination pending recovery of the subject.
- Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of RV GE.
- Concurrently participating in another clinical study, at any time during the study period in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

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 during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids are allowed).
- Administration of immunoglobulin 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

The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine/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 8.7):

- Known hypersensitivity after previous administration of HRV vaccine or to any component of the vaccine.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following AEs constitute contraindications to administration of HRV vaccine/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).

- Acute severe febrile illness.
- Diarrhoea or vomiting.

5. STUDY CONDUCT CONSIDERATIONS

5.1. Ethics and regulatory considerations

5.1.1. Clinical Trial Notification (CTN) to Regulatory Authority

GSK Biologicals' will submit the clinical trial notification (CTN) to the regulatory authorities in accordance with Article 80-2 of the Pharmaceutical Affairs Law prior to a site initiating the study in Japan.

5.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with the Declaration of Helsinki [(South Africa, 1996), Appendix A], Articles 14-3 and 80-2 of the Pharmaceutical Affairs Law, Good Clinical Practice (GCP) (MHW Ordinance No.28, March 27, 1997) and Revised GCP (MHLW Ordinance No.106, June 12, 2003), while ensuring the protection of human subjects.

The scientific rationale for and ethical conduct of the study should be reviewed and approved by the Institutional Review Board (IRB). If the protocol, informed consent form, or any other information that the IRB has approved is amended during the study, the IRB must review and approve these amended documents. Any revised informed consent form and any other information should receive the IRB's approval in advance of use for the enrollment of new subjects.

The investigator and GSK should provide the head of the medical institution with the current protocol, informed consent form and other written information, Investigator Brochure (IB), and other documents to be reviewed by the IRB. The head of the medical institution will submit these documents to the IRB before he/she approves the conduct of the study.

After the IRB makes a decision on whether the study may be conducted or not and notifies it to the head of the medical institution, the head of the medical institution will give his/her instruction or notify his/her decision in writing based on the IRB's decision to the investigator and sponsor together with the IRB's dated document on its decision. If the IRB disapproves of the conduct of the study, the head of the medical institution must not approve it.

The investigator and the head of the medical institution agree to allow the IRB direct access to all relevant documents.

The IRB must be constituted in accordance with all applicable regulatory requirements.

5.1.3. Informed Consent of Subjects

Informed consent will be obtained from the parents/guardians of the subjects before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

While informed consent information can be presented to groups at an initial information session, parents/guardians of each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

5.1.3.1. Informed Consent

Prior to the start of the study, the investigator/sub-investigator should fully inform the parents/guardians of potential subject of the study including the written information given approval by the IRB. The investigator/sub-investigator should provide the parents/guardians of subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. After giving informed consent based on his/her free will, the parents/guardians of the subject should sign and personally date the consent form. The person who conducted the informed consent discussion should sign and personally date the consent form. If the parents/guardians of the subject are unable to read, an impartial witness should be present during the entire informed consent discussion, and the witness should sign and personally date the consent form. The investigator/sub-investigator should retain this signed and dated form and other written information together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the parents/guardians of the subjects should include explanations of the following:

a. That the study involves research.

b. The purpose of the study.

c. The methods of the study (those aspects of the study that are experimental, inclusion criteria, the probability for random assignment to each treatment in a randomisation study).

d. The expected duration of the subject's participation in the study.

e. The approximate number of subjects involved in the study.

f. The reasonably foreseeable benefits and risks or inconveniences to the subject.

g. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

h. The compensation and/or treatment available to the subject in the event of study-related injury.

i. That the subject's participation in the study is voluntary and that the parents/guardians of the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

j. That the parents/guardians of the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

k. The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.

l. That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the parents/guardians of the subject is authorising such access.

m. If the results of the study are published, the subject's identity will remain confidential.

n. The anticipated expenses, if any, to the subject for participating in the study.

o. The anticipated prorated payment, if any, to the subject for participating in the study.

p. Name, title, and contact address of the investigator/sub-investigator.

q. The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.

r. The responsibilities of the subjects' parents/guardians.

5.1.3.2.Revision of informed consent form and other written information.

If information becomes available that may be relevant to the parents/guardians of the subject's willingness to continue participation in the study, the investigator/sub-investigator should immediately inform the parents/guardians of the subject of it to

confirm the willingness to continue participation in the study, and document the communication of this information (in medical records). If necessary, the investigator should revise the written information to be provided to the parents/guardians of the subjects, promptly report it to the sponsor, and obtain approval from the IRB. The investigator should not enroll any new subject in the study before the IRB's approval. After the IRB approves the revision of the written information to be provided to the parents/guardians of the subjects, the investigator/sub-investigator should inform the parents/guardians of each subject participating in the study of the revised written information, and obtain written informed consent.

5.1.4. Investigator Reporting Requirements

As indicated in section 8.9 (Regulatory Reporting Requirements for SAEs), the investigator is responsible for reporting all SAEs to the head of the medical institution. Furthermore, the investigator is responsible for reporting the summary status of the study in writing annually or more frequently if requested by the IRB to the head of the medical institution for continuing review by the IRB. The investigator is also responsible for notifying the head of the medical institution of the termination, suspension, or completion of the study.

5.2. General study aspects

5.2.1. Routine vaccinations

DTPa and HBV vaccines are allowed to be co-administered along with HRV vaccine/Placebo. Administration of all routine childhood vaccinations since birth up to Visit 3 must be documented in the eCRF.

5.2.2. Feeding

There are no restrictions on feeding, neither before nor after HRV vaccine/Placebo administration.

5.2.3. Surveillance of GE leading to medical intervention and collection of GE stool samples

Active follow-up for occurrence of GE leading to medical intervention will be conducted during the period starting from administration of Dose 1 up to the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or Placebo until end of study visit, the intention is to make contact with each subject's parent/guardian at least once every two weeks to check on the occurrence of any GE leading to medical intervention. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or health care workers or other convenient means. 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 leading to medical intervention 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 leading to medical intervention 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.

Parents/guardians should be instructed to collect stool sample(s) from the subject if the subject develops GE leading to medical intervention during the entire study period. Refer to the glossary of terms for definition of diarrhoea/GE. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of the GE episode. A stool sample should be collected for each GE episode. A second stool sample should be collected if the first sample is insufficient. Two occurrences of GE should be classified as separate episodes, if there are 5 or more diarrhoea-free days between the episodes.

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 consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.4. Outline of study procedures

Table 1 presents the outline of study procedures.

Table 1 List of study procedures

Age	6-14 weeks			One year	Two years
Visits Timing Sampling time point	VISIT 1 Day 0 Pre-vacc	VISIT 2 Month 1	VISIT 3 Month 2 Post-vacc 2	VISIT 4	VISIT 5
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	●	●	-	-	-
Randomisation	●	-	-	-	-
Blood sampling (1 ml) for antibody determination in an immunogenicity subset *	●	-	●	-	-
Study vaccination (HRV vaccine/ Placebo)	●	●	-	-	-
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians	●	●	-	-	-
Return of reactogenicity diary card	-	○	○	-	-
Transcription of the reactogenicity diary card		●	●	-	-
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●	-	-
Record any concomitant medication/vaccination, by investigator	●	●	●	●#	●#
Recording of GE leading to medical intervention occurring throughout the study period	●	●	●	●	●
Contact the subject's parent/gardian to check GE occurrence at least every two weeks	○	○	○	○	○
Collection of stool samples if subject has GE leading to medical intervention	●	●	●	●	●
Return of GE diary card	-	○	○	○	○
GE diary card transcription	-	●	●	●	●
Recording of SAEs	●	●	●	●	●
Reporting AEs leading to drop-out	●	●	●	●	●
Conclusion at Visit 4				●	
Study conclusion	-	-	-	-	●

Note: Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Blood sampling will be done only from subjects in the immunogenicity subset (N = 60).

for concomitant medication administered for the treatment of an AE leading to drop-out/SAE.

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed.

Table 2 Intervals between study visits

Interval /Visit	Range of interval /Visit
Visit 1→Visit 2	30 - 48 days
Visit 2→Visit 3	30 - 48 days
Visit 4	1 year of age ± 15 days
Visit 5	2 years of age ± 15 days

N.B: The reference date for intervals between study visits: the first vaccination date

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 clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E .

The detailed description of procedures to be performed during each study visit is presented below:

Visit 1 (Day 0): Dose 1 of the HRV vaccine/Placebo (at 6 -14 weeks of age)

- Written informed consent obtained from the parents/guardians of the subject.
- Checking inclusion/exclusion criteria (refer to section 4.2 and 4.3).
- Checking of contraindications to vaccination (refer to section 4.5).
- Recording of medical history and physical examination.
- Recording of pre-vaccination body temperature (measured by an axillary thermometer).
- Measurement of height and weight.
- Recording of feeding practice.
- Random allocation of the subjects into one of the two study groups.
- Collection of blood sample from subjects in the immunogenicity subset (N = 60) for serology prior to vaccination: a minimum of 1 ml of whole blood will be withdrawn to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Vaccination:
  - Study vaccination: HRV vaccine/Placebo.

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 the HRV vaccine/placebo.

- Diary cards will be provided to the parents/guardians of all subjects to record information on solicited symptoms (fever, fussiness/irritability, loss of appetite cough/runny nose, diarrhoea and vomiting) occurring on the day of Dose 1 and the following 7 days, on any medications and unsolicited AE occurring within 31 days after Dose 1, as well as on any GE leading to medical intervention occurring until Visit 2. The parents/guardians should be instructed to return the completed diary card to the investigator at Visit 2.
- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- The subjects' parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 1 and 2. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- Recording of any prior/concomitant medication (including vaccinations) administered.
- Recording of SAEs.

Visit 2 (Month 1): Dose 2 of the HRV vaccine/Placebo

- Checking elimination criteria (refer section 4.4).
- Checking contraindications to vaccination (refer to section 4.5).
- Recording of concomitant medication/vaccination administered.
- Physical examination.
- Recording of pre-vaccination of body temperature (measured by axillary thermometers)
- Recording of feeding practice.
- Collection and verification of diary card containing information on solicited symptoms/medication/adverse events/GE leading to medical intervention occurring from Visit 1 till Visit 2. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.

- Vaccination:
  - Study vaccination: HRV vaccine/Placebo.

  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 the HRV vaccine/placebo.
- Diary cards will be provided to the parents/guardians of all subjects to record information on solicited symptoms (fever, fussiness/irritability, loss of appetite cough/runny nose, diarrhoea and vomiting) occurring on the day of Dose 2 and the following 7 days, on any medications and unsolicited AEs occurring within 31 days after Dose 2 as well as on any GE leading to medical intervention occurring until Visit 3. The parents/guardians should be instructed to return the completed diary card to the investigator at Visit 3.
- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- The subjects' parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 2 and 3. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording of SAEs.
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.

Visit 3 (Month 2): Follow-up visit

- Physical examination.
- Checking elimination criteria (refer section 4.4).
- Recording of any concomitant medication/vaccination administered.
- Collection of post-vaccination blood sample from subjects in the immunogenicity subset (N = 60): a minimum of 1 ml of whole blood will be withdrawn to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Collection and verification of diary card containing information on solicited symptoms/medication/adverse event/GE leading to medical intervention occurring from Visit 2 till Visit 3. The investigator will verify the diary card and transcribe the

information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.

- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 3 and 4. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- A "GE diary card" will be provided to parents/guardians of all subjects and will be used by the study staff during contact visits to record information on any GE episodes leading to medical intervention occurring until Visit 4. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording of SAEs.
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.
- All parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 4 (One year of age): Follow-up Visit

- Physical examination.
- Checking elimination criteria (refer section 4.4).
- Collection and verification of GE diary card containing information on GE leading to medical intervention occurring from Visit 3 till Visit 4. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.
- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 4 and 5. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- A "GE diary card" will be provided to parents/guardians of all subjects and will be used by the study staff during contact visits to record information on any GE episodes leading to medical intervention occurring until Visit 5. The

parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.

- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording of any concomitant medication for the treatment of an AE leading to drop-out/SAE.
- Recording of SAEs.
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.
- All parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Conclusion at Visit 4.

Visit 5 (Two years of age): Follow-up Visit

- Physical examination.
- Checking of elimination criteria.
- Collection and verification of GE diary card containing information on GE leading to medical intervention occurring from Visit 4 till Visit 5. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.
- Recording of SAEs.
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.
- Recording of any concomitant medication for the treatment of an AE leading to drop-out/SAE.
- Study conclusion.

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

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

GE stool analysis

Stool samples collected during each GE episode leading to medical intervention from Visit 1 until Visit 5 will be tested at GSK Biologicals or a laboratory designated by GSK Biologicals using ELISA to detect RV. If positive, the sample will be tested by polymerase chain reaction (PCR) to determine the G and the P genotypes. If any G1 RV is detected, vaccine virus will be differentiated from the wild type serotype by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) followed by reverse hybridisation assay or an equivalent approach (Refer Appendix F).

Serum analysis

Serum obtained from whole blood samples collected from subjects in the immunogenicity subset at Visit 1 and Visit 3 will be tested by ELISA at GSK Biologicals' central laboratory (or validated laboratory designated by GSK Biologicals) to measure serum anti-rotavirus IgA antibody concentrations (refer Appendix F). The assay cut-off is 20 U/ml.

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

Table 3 presents the laboratory assays with their cut-off.

Table 3 Laboratory Assays

Antibody	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Core Laboratory
Rotavirus IgA	ELISA	In-house	U/ml	20	GSK Biologicals, Rixensart*

ELISA: Enzyme-linked immunosorbent assay
U/ml: units/millilitre
* GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals

5.6.3. Immunological read-outs

Table 4 presents the immunological read-outs for the study.

Table 4 Immunological read-outs

Sampling time point			Marker	Number of subjects
Timing	Month	Visit number		
Serology (in a subset of subjects [N = 60])				
Pre	Day 0	1	HRV IgA	60
Post-vacc 2	Month 2	3	HRV IgA	60
GE stool analysis				
From Visit 1 to Visit 5			RV antigen	All

Additional analysis (Amended, 07 May 2007)

If deemed necessary by the investigator, additional analysis on other tissues/fluids (e.g. cerebrospinal fluid in case of meningitis) may be performed by GSK Biologicals' designated laboratory.

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject.

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests.

It may be that any findings in the present study necessitates further investigation by GSK Biologicals into the efficacy or immunogenicity of the HRV vaccine and its constituents under study.

Refer also to protocol Appendix B, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

The lyophilised formulations of HRV vaccine/Placebo to be used has been developed and manufactured by GSK Biologicals. The Quality Control Standards and Requirements for the candidate vaccine are described in separate release protocols and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

Table 5 gives the detailed formulation of the HRV vaccine/Placebo.

Table 5 Composition of the GSK Biologicals' HRV lyophilised vaccine and Placebo

Vaccine	Formulation	Presentation	Volume
LYOPHILISED FORMULATION			
GSK Biologicals' HRV lyophilised vaccine	RIX4414 HRV strain at least $10^{6.0}$ $CCID_{50}$ Dulbecco's Modified Eagle Medium (DMEM) 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised vaccine in a monodose glass vial Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' Placebo for HRV lyophilised vaccine	DMEM 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised Placebo in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals. calcium carbonate buffer	Calcium carbonate 60 mg/ml Xanthane 0.25% in 1.0 ml water for injection	Liquid buffer in prefilled syringe	at least 1.1 ml

Refer Appendix G for details of vaccine supplies.

6.1. Dosage and administration

6.1.1. Lyophilised formulation of HRV vaccine/Placebo

To prepare GSK Biologicals' HRV lyophilised vaccine/Placebo for administration, the entire content of the supplied diluents (calcium carbonate buffer) should be transferred from the oral applicator into the vial of the lyophilised product (HRV vaccine/Placebo) via the intermediate device. The vial should be shaken well to resuspend the vaccine. The entire volume of the resuspended product (approximately 1 ml) should be withdrawn into the same oral applicator and the resuspended product should then be administered promptly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration should occur in a quiet environment. Sufficient time should be allowed for the baby to swallow the vaccine/Placebo, to avoid regurgitation or vomiting. Should however 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 in the study.

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.

The vaccination regimen is summarised in Table 6.

Table 6 Dosage and Administration

Visit	Vaccination	Dose	Vaccine	Route
1, 2	Rotavirus/Placebo	1	Lyophilised HRV vaccine/ Placebo	Oral

All vaccines administered should be documented in the eCRF.

6.2. Storage

All investigational products to be administered to subjects must be stored in a safe and locked place with no access by unauthorised personnel.

Vaccines will be stored at the defined temperature range (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 monitoring device will be used as a back up device and it will be opened in case of any 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 monitoring device), 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 after the alarm is activated.

It is also required to place a validated freezing point indicator 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.

6.3. Vaccine accountability

The head of the medical institution is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the head of the medical institution or the storage manager must maintain investigational product accountability records throughout the course of the study. The storage manager will document the amount of investigational product received from and returned to GSK, the amount supplied and/or administered to and returned by subjects, if applicable. For more details see Appendix G.

6.4. Treatment allocation and randomisation

Target enrolment will be 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the Placebo Group) to obtain 612 evaluable subjects (408 subjects in the HRV lyophilised vaccine group and 204 subjects in the Placebo Group) for the evaluation of the primary objective.

The actual treatment number used for first vaccination of the subject must be recorded by the investigator in the eCRF (Randomisation/Treatment Allocation Section).

6.4.1. Randomisation of supplies

A randomisation 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 randomisation 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, 5% over-randomisation of supplies will be prepared.

The vaccine doses will be distributed to each study centre, respecting the randomisation block size.

6.4.2. Randomisation of subjects

The treatment allocation at the investigator site will be performed using a central randomisation system on Internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for centre.

After having checked that a subject is eligible, the person in charge of the vaccination will access the randomisation system on Internet. Upon providing a subject number for

the subject, the randomisation system will use the minimisation algorithm to determine the treatment number to be used for the subject.

Would internet be unavailable the subjects would be administered the vaccine number with the highest number still available at the vaccination site.

6.4.3. Subset for immunogenicity

A subset of 60 subjects will be part of the immunogenicity subset. Due to foreseeable difficulty in obtaining consent for withdrawal of blood from subjects, only those subjects whose parents/guardians consented will be enrolled in this immunogenicity subset. This subset will be centre specific and not all the centres will enrol subjects in to this subset. All subjects in this subset will provide blood samples to explore immunogenicity of the HRV vaccine/Placebo.

6.5. Method of blinding and breaking the study blind

The study will be conducted in a double-blind manner with respect to HRV vaccine and placebo. The parents/guardians of the subjects, the study personnel and the investigator will be unaware of the study vaccine administered (HRV vaccine or placebo). Blinding will be maintained for the whole study period. If the final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period, access to the individual treatment decode during the final analysis will be limited to the statistician and the database administrator to maintain double blinding until study end. This will allow unbiased evaluation of the study vaccine.

The investigator, or person designated by the investigator, should contact GSK Biologicals' Central Safety physician directly or via the local safety contact (see below and Study Contact for Emergency Code Break in Sponsor Information page) to discuss the need for emergency unblinding. The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) 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.

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which is unexpected and attributable/suspected, prior to regulatory reporting. The Clinical Safety physician is responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (Refer to Section 8.9).

GSK Biologicals Clinical Safety Physician (Study Contact for Emergency Code Break)
Tel: [redacted] Fax: [redacted] or [redacted] Mobile phones for 7/7 day availability: [redacted] (Head Safety Evaluation and Risk Management Paediatric) Back-up mobile phone contact: [redacted]

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-randomisation 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 randomisation 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 randomised 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 31 days after each dose of study vaccine 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 or at any time during the study period up to Visit 3 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.

Any vaccine not foreseen in the study protocol administered since birth up to Visit 3 is 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 [Axillary temperature <37.5°C (99.5°F)] 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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form. Refer to Section 8.2 for definition of SAE.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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.

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 vaccination) 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 hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation 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 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 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 hospitalisation.

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. vital signs) 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not 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 HRV vaccine/Placebo must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity 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 intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at randomisation or the first receipt of the HRV vaccine/Placebo and will end at the last study visit (i.e. Visit 5) following administration of the last dose of the HRV vaccine/Placebo for each subject. See Section 8.8 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK 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 and throughout the follow-up phase as appropriate.

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.

When an AE/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/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/SAE screens in the eCRF. 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.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.8.2 for details of the back-up reporting system.

8.5.1. Solicited adverse events

Solicited general AEs

Solicited adverse events will be evaluated during an 8-day follow-up period (Day 0 to Day 7) after each HRV vaccine/Placebo dose. Diary cards will be provided to the parents/guardian's of the subject to record the symptoms observed.

The general adverse events solicited in this study is listed below

Fever (axillary)
Irritability/Fussiness
Diarrhoea
Vomiting
Loss of appetite
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 7:

Table 7 Intensity scales to be used by the parents/guardians for solicited symptoms

Adverse Event	Intensity grade	Parameter
Fever*		Record temperature in °C using an axillary thermometer
Fussiness/Irritability	0 1 2 3	Behaviour as usual Crying more than usual/no effect on normal activity Crying more than usual/interferes with normal activity Crying that cannot be comforted/prevents normal activity
Diarrhoea¶		Record the number of looser than normal stools/day
Vomiting§		Record the number of vomiting episodes/day
Loss of appetite	0 1 2 3	Normal Eating less than usual/no effect on normal activity Eating less than usual/interferes with normal activity Not eating at all
Cough/runny nose	0 1 2 3	Normal Cough/runny nose which is easily tolerated Cough/runny nose which interferes with daily activity Cough/runny nose which prevents daily activity

*Fever is defined as temperature ≥ 37.5°C as measured by an axillary thermometer.
¶Diarrhoea 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 diarrhoea, fever and vomiting occurring during the solicited 8-day follow-up period will be scored at GSK Biologicals as described in Table 8.

Table 8 Intensity scales used at GSK Biologicals' for diarrhoea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	Intensity grade	Parameter
Diarrhoea	0 1 2 3	Normal (0-2 looser than normal stools/day) 3 looser than normal stools/day 4-5 looser than normal stools/day ≥ 6 looser than normal stools/day
Vomiting	0 1 2 3	Normal (no emesis) 1 episode of vomiting/day 2 episodes of vomiting/day ≥ 3 episodes of vomiting/day
Fever	0 1 2 3	Temperature axillary < 37.5°C Temperature axillary ≥ 37.5 – ≤ 38.0°C Temperature axillary > 38.0 – ≤ 39.0°C Temperature axillary > 39.0°C

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including 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 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 utilised 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 submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information 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 other AEs should be assessed by the investigator using the following question:

"Is there a reasonable possibility that the AE (or SAE) may have been caused by the investigational product?"

NO	:	The AE 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.
YES	:	There is a reasonable possibility that the vaccine contributed to the AE.

When new information is received, the causality will be reviewed and updated, if necessary.

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. 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 (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

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, if applicable
- Erroneous administration
- Other cause (specify).

8.6.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences (including gastroenteritis), the subject's parents/guardians will be asked if the subject 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 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 AEs 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, stabilised, 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 recognised 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 screens in the eCRF. The updated screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.8.1.

For cases of IS, the investigator will document all available information on the Serious Adverse Event pages contained in the individual eCRF, as well as on the IS form.

The Standard Verbal Autopsy Questionnaire (see Appendix H) [World Health Organization] should be completed whenever possible 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 an autopsy is performed or not. The Standard Verbal Autopsy Questionnaire does not replace the written autopsy report.

In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.8.2. for details of the back-up reporting system.

Outcome of any non-serious AE 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

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

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 will complete and submit relevant information on the SAEs in the SAE screens in eCRF **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 completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting via a GSK local operating company. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional 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, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours as outlined in Section 8.8.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. 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 SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received 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.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 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, 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. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper 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.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.8.1.

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF/sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

Study Contact for Reporting SAEs
GlaxoSmithKline K.K Development & Medical Affairs Division, Sec. 2, Clinical Monitoring Dept. 2 [redacted] 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [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] (Head Safety Evaluation and Risk Management Paediatric) 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 fulfil specific regulatory and 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 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.

After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.

8.11. 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.

8.12. Assessment of GE episodes leading to a medical intervention

Any GE episode (defined as diarrhoea with or without vomiting) leading to a medical intervention 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 temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given. 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 doctor visit, emergency room visit or hospitalisation) will also be recorded for each GE episode.

In the 20-point scoring system, points will be 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 will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 9.

Table 9 The 20-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	2
≥ 6	3
Maximum number of looser than normal stools /24 hours	
1-3	1
4-5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2-4	2
≥ 5	3
Fever∗	
Axillary	
36.6 – 37.9°C	1
38.0 – 38.4°C	2
≥ 38.5°C	3
Dehydration	
1-5%	2
≥ 6%	3
Treatment	
Rehydration	1
Hospitalisation	2

∗ 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.

Periodic contact will be made with the subjects' family to enquire about the occurrence of GE leading to a medical intervention. Collection of a stool sample will be requested if not yet provided and if GE occurred since last contact. For an GE considered to be an SAE, the SAE screen/form in the eCRF is completed.

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 because of 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 8.7).

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/was not available for 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 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 leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

10.2. Secondary endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- 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/Placebo.
- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Immunogenicity (in the immunogenicity subset N = 60)

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 3.

10.3. Estimated sample size

The primary objective is to determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Target enrolment will be 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the Placebo Group) to obtain 612 evaluable subjects (408 subjects in the HRV lyophilised vaccine group and 204 subjects in the Placebo Group) with an attrition rate of 20% of non-evaluable subjects for the evaluation of the primary objective.

Considering a 2:1 randomisation ratio and various incidence rates, Table 10 provides the power that the 95% CI for vaccine efficacy (VE) will be above 0% and 10%.

Therefore, for an 8% attack rate (AR) of RV GE leading to a medical intervention in the Placebo Group from 2 weeks after Dose 2 up to 2 years of age, and if the VE is truly 80%, the study has 92% power to observe a 95% CI for the VE that will be above 10%. It is expected to observe a total of 28 RV GE leading to a medical intervention during the efficacy follow-up period in the Total Vaccinated Cohort.

In Japan, medical intervention risk due to RV GE is reported in 50% of children until 6 years of age which is not the school age. Supposing that the 50% risk is observed every year, it can be calculated that AR of the annual RV GE is 8.3% (50/6). The RV GE cases reported in 2005/2006 season seems to be low compared with those in past years. We have estimated that AR of RV GE during the 2 years is 8% considering yearly fluctuation of AR.

Table 10 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 612 evaluable subjects - 408 subjects in HRV group and 204 subject in the Placebo Group, power based on 1.000 simulations using Proc StatXact)

Incidence rate in the Placebo for any RV GE leading to a medical intervention	VE (%)	Power to have a lower limit of the 95%CI on VE ≥ 0%	Power to have a lower limit of the 95%CI on VE ≥ 10%
10%	80%	97%	96%
	70%	90%	83%
8%*	80%**	94%	92%
	70%	82%	74%
7%	80%	90%	86%
	70%	75%	67%
5%	80%	76%	69%
	70%	59%	50%

* anticipated rate in the Placebo for any RV GE leading to a medical intervention
**anticipated vaccine efficacy

10.4. Study cohorts to be evaluated

10.4.1. 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 from the immunogenicity subset for whom immunogenicity data are available.
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects.

10.4.2. ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects:

- who received two 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,
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks after Dose 2 of HRV vaccine or placebo,
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

10.4.3. 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,
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

10.4.4. 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 time point.
- 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 10.5 for definition of seronegative subjects.

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 vaccinated 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 vaccinated subjects are excluded from the ATP immunogenicity cohort. In such a case, the total vaccinated cohort analyses will evaluate whether exclusion from the ATP cohort could 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.

Safety

Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be re-assessed to ensure more accurate reporting of study data by further analysis.

Immunogenicity

The cut-off value of anti-rotavirus IgA antibody is defined by the laboratory before the analysis and is described in Section 5.6.2.

- A seronegative subject is a subject whose titre is below the cut-off value.
- A seropositive subject is a subject whose titre is greater than or equal to the cut-off value.
- Seroconversion is defined as the appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.

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.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

10.6. Final analyses

Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

10.6.1. Analysis of demographics

The mean, range and standard deviation of height in centimetre (cm), weight in kilogram (kg) and of age in weeks will be calculated per group. The racial and gender composition per group will also be presented.

The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group.

Summary of feeding practice 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 against:

- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to G1 serotype caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to non-G1 serotypes during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE of any aetiology leading to a medical intervention, efficacy against hospitalisation due to GE of any aetiology, efficacy during the period starting from two weeks after Dose 2 until Visit 4).

10.6.3. Analysis of safety

The overall incidence, with exact 95% CI, of any adverse events (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each 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.

The verbatim reports of unsolicited adverse events will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will

be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited adverse events occurring within 31-day follow-up period after any doses with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited adverse events rated as grade 3 and for unsolicited adverse events with causal relationship to vaccination.

Serious adverse events reported during the study period will be described in detail.

10.6.4. Analysis of immunogenicity

In a subset of subjects (N = 60)

For each treatment group, at each time point that anti-rotavirus IgA is measured,

- Seroconversion/seropositivity and their exact 95% CI will be calculated.
- GMCs 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 (RCCs).

The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between HRV vaccine and Placebo groups will be computed.

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. STUDY PERIOD

May 2007 –December 2009.

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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 aetiology 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 recognised 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 minimise 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 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 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

A Deviations from Protocol

The investigator/sub-investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without agreement by the sponsor or prior IRB approval. As soon as possible, the implemented deviation or change and the reasons for it should be submitted to the head of the medical institution and the IRB for approval, and via the head of the medical institution to the sponsor for agreement.

The investigator/sub-investigator should document and explain any deviation from the approved protocol, submit the document and retain its copy.

B Changes of Protocol

1. If it becomes necessary to make any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects, the sponsor should promptly document the changes and reasons for them and amend the protocol after discussion with the coordinating investigator and the medical expert, and notify the heads of the medical institutions and investigators of the changes of the protocol (sample informed consent form and other written information, if necessary). The investigator should not implement any significant changes without approval from the IRB.
2. For changes other than the above 1), the sponsor should document the changes and reasons for them and inform the heads of the medical institutions and investigators of the changes of the protocol. Such changes require prior approval from the IRB, except where necessary to eliminate an immediate hazard(s), or when the change(s) involves only logistical or administrative aspects of the study. The investigator should promptly report the changes implemented without prior approval to the IRB for approval.
3. 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.
4. Submission of 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 amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator and site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicentre studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss this with the investigator and the head of the medical institution, including the reasons for taking such action, at that time. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

GSK will promptly inform all other investigators and the head of the medical institution, and/or institutions conducting the study if the study is suspended or terminated for safety reasons. GSK will also promptly 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 and the head of the medical institution must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

Reasons for suspension or early termination will be documented in the study file at GSK Biologicals. 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

By monitoring the parties involved in the study including medical institutions, investigators, sub-investigators, study collaborators, and storage managers, monitors:

1. Oversee the process of obtaining written informed consent, the control of investigational products and the progress of the study (including withdrawals and adverse events, and ensure that the conduct of the study is in compliance with the "Good Clinical Practices" (GCP) (MHW Ordinance No.28 dated 27 March 1997), this protocol, and any other written agreement between the sponsor and the investigator/institution.
2. Collect and provide information that is necessary to conduct the study properly (information on investigational products' safety, efficacy and quality).
3. Verify that the investigator has adequate qualifications and resources and remain adequate throughout the study period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the study and remain adequate throughout the study period.
4. Verify that source documents and other study records are accurate, complete, kept up-to-date and maintained.
5. Determine whether the person responsible for retaining records is maintaining the essential documents at each medical institution.
6. Check the accuracy and completeness of the eCRF entries, source documents and other study-related records against each other.

7. The monitor will perform an eCRF review and a Source Document verification (verify eCRF/RDE entries 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).
8. 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.
9. Make clarifications to eCRFs in accordance with the standard clarification agreement (SCA).

The investigator and institution should agree to allow the monitor direct access to essential documents and other relevant documents. Direct access to essential documents by monitors and the scope of those documents will be specified separately in the written procedures for monitoring prepared for this study. Details of the standard clarification agreement (SCA) will be specified separately in the written procedures for SCA discussed and approved by the monitor and the investigator.

VI. Archiving of Data

A Records Retention

Following closure of the study, the investigator or the head of the medical institution (if applicable) 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).

The persons responsible for retaining records designated by the medical institution should maintain essential documents, including subject's medical records, laboratory data, records of IRB review, contract, records of informed consent, and records of investigational products control at the medical institution as required by the GCP for one of the following periods 1) or 2), whichever is longer. However, if the sponsor needs to retain these documents for a longer period, the period and methods of retention should be discussed with the sponsor. The person responsible for retaining records will be designated for each type of records. The sponsor will inform the head of the medical institution in writing as to when these documents no longer need to be retained.

1. until manufacturing (import) approval is granted on the investigational product (or for 3 years after the formal discontinuation of clinical development of the investigational product)
2. for 3 years after discontinuation or completion of the study

B Provision of Study results and Information to Investigators

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, GSK will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the subjects, as

appropriate. In addition, the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at a GSK site or other mutually agreeable location.

GSK will provide the investigator with the randomization codes for their site after the statistical analysis for the entire study has been completed.

VII. Data Management

Subject data are collected by the investigator or designee using the eCRF defined by GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Any change or correction to eCRF entries will be made through the Data Clarification Request (DCR) if such action is needed after the eCRF is retrieved by GSK. Database freeze will occur when data management quality control procedures are completed. Original eCRFs and DCRs will be retained by GSK, while the investigator will retain a copy.

Data management staff may make clarifications to eCRFs as defined in the SCA. Details of the SCA will be specified separately in the written procedures for SCA discussed and approved by the monitor and the investigator.

VIII. Quality Control, Quality Assurance and Audits

A Quality Control

The sponsor's sections involved in the study, including monitoring, archiving, investigational product control, data management, and statistical analysis will perform quality control in compliance with their respective standard operating procedures prepared by the sponsor, and maintain records of quality control.

B Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

C 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's 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.

IX. 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 study will be conducted in multiple centres in Japan.
- Target enrolment will be 765 eligible subjects.
- Recruitment will be terminated when 765 eligible subjects have been enrolled.
- The intended duration of the study, per subject, will be till the time that the subject is two years of age.
- 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 (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. 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**

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 minimise the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. **Serum separation**

These guidelines aim to ensure high quality serum by minimising the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

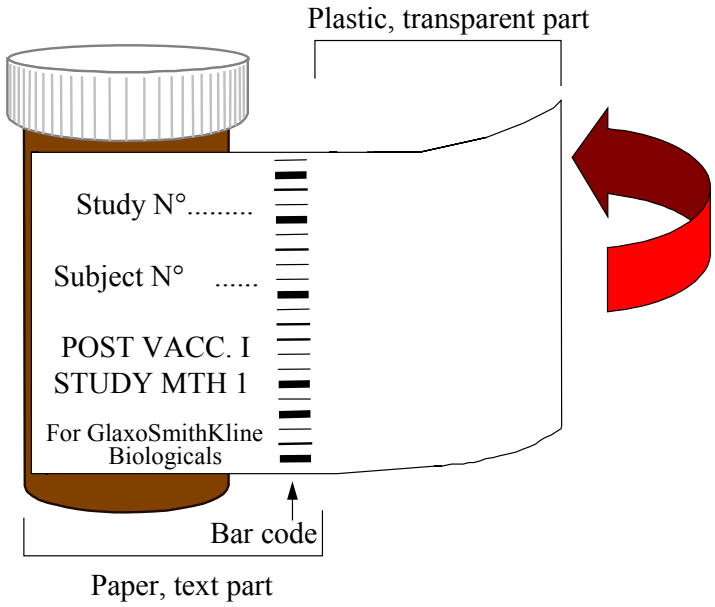
- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for ten minutes. Error in 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).

3. **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.



- Labels should not be attached to caps.

4. **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 Biological 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 serum samples.
- Once shipment 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 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.

1. Collection

Containers/8 ml tubes/ziplock bags and fridge envelopes will be provided to parents/guardians for collection of stool samples for planned stools subset and during any GE episodes. Parents/guardians will be asked to preferably use the containers to collect

[1] The Biological Specimen 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.

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/8 ml tubes/ziplock bag label with a black ink or ballpoint pen and return the collected stool samples to the study personnel. Subject number will be used for stool sample identification.
- If necessary, any hand-written additions to the labels by the study personnel should be made using indelible ink.

3. Preparation of aliquots

- Stool samples collected during gastroenteritis episode leading to medical attention will be processed at study site/local laboratory to prepare aliquots in 8ml tubes. Please note, if sufficient stool sample is available a back-up sample should be retained at the study site.

4. Sorting and storage

- The stool 8 ml tubes 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 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.
- 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.

GLAXOSMITHKLINE BIOLOGICALS

Biospecimen reception
Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart – Belgium

Telephone: [redacted]

Fax: [redacted]

Appendix E Shipment of Biological Samples

Instructions for Shipment of Serum/Stool Samples

Biospecimen 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.

Biospecimen samples must be placed with dry ice (maximum -20°C) in a container complying with International Air Transport Association (IATA) requirements if shipment by air or complying with ADR or local regulations if transport by road. The completed standard Biological Specimen 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).

The airway bill should contain the instruction for storage of samples at maximum -20°C.

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.

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

Serum Analysis

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 millilitre (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 et al. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet. 1999; 354:287-90.

GE stool analysis

1. Antigen Detection in GE stool samples

Rotavirus antigen in GE episodes will be detected by ELISA.

2. RV strain typing

Targeted RV gene will be amplified by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) to generate RV cDNA fragments. The genotype will be confirmed by reverse hybridization using serotype-specific DNA probes and/or by direct sequencing of the amplified RV cDNA product.

This genotyping analysis can be completed with the determination of the P-genotype 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 study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- HRV vaccine in monodose vials.
- Placebo in monodose vials.
- Diluent (calcium carbonate buffer) in pre-filled syringes.

At least 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).

Additional doses will also be supplied for over-randomisation.

All monodoses vials/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 time point. Each label will contain the following information: study number, identification number for the subject , sampling time point , and timing .

Other supplies provided by GSK Biologicals:

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:

- tubes with screw caps for serum samples,
- racks and cardboard boxes for the tubes of serum.
- Supply for stool collection

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 from local country medical department to investigational site**

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : [redacted]
E-mail: [redacted]

In case of any temperature deviation, the official written approval for the use of vaccine must be obtained from GSK.

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 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 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 GSK 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.

Appendix H Standard Questionnaire for Verbal Autopsy

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).

The document is supplied as a separate PDF file.

Appendix I Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007
Co-ordinating author:	[redacted]
Rationale/background for changes: The protocol has been amended as per the request from Pharmaceutical and Medical Devices Agency (PMDA), Japan.	

Text has been deleted in the following section:
Section 5.6.3: Immunological read-outs:
Additional analysis:

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests. ~~the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.~~

It may be that any findings in the present study ~~or in other studies~~ necessitates further investigation by GSK Biologicals into the efficacy or immunogenicity of the ~~vaccine.~~ HRV vaccine and its constituents under study. ~~or further research in the disease under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.~~

~~A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.Any sample testing will be done in line with the consent of the individual subject's parents/guardians.Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.~~

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007

Approved by:

Director,
Worldwide Clinical Development,
Rotavirus vaccine, [redacted] dd-mm-yyyy

Deputy Director,
Clinical Development,
GlaxoSmithKline K.K. [redacted] dd-mm-yyyy

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Annex 2

Standard Verbal Autopsy Questionnaire

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

CONFIDENTIAL

Rota-056 (107625)

GlaxoSmithKline

Sponsor:
GSK Building
6-15, Sendagaya 4-chome
Shibuya-ku, Tokyo 151-8566
Japan

Study vaccine number	444563
Study vaccine	Lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	107625 (Rota-056)
Date of approval	Final: 30 March 2007
Title	Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Rotavirus Vaccine • [redacted] Central Study Co-ordinator • [redacted] Central Study Co-ordinator • [redacted] Statistician • [redacted] Manager, Clinical Development

Approval of Sponsor signatories

Sponsor signatory:

[redacted]
Director,
Worldwide Clinical Development,
Rotavirus vaccine,
GSK Biologicals.

[redacted]
Deputy Director,
Clinical Development,
GlaxoSmithKline K.K.

Signature: [redacted]

Date: 11 Apr 2007

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GSK Biologicals' Protocol DS V 12.1

30-MAR-2007
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CONFIDENTIAL

Rota-056 (107625)

Sponsor:
GSK Building
6-15, Sendagaya 4-chome
Shibuya-ku, Tokyo 151-8566
Japan

Study vaccine number	444563
Study vaccine	Lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	107625 (Rota-056)
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Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Rotavirus Vaccine • [redacted] Central Study Co-ordinator • [redacted] Central Study Co-ordinator • [redacted] Statistician • [redacted] Manager, Clinical Development

Approval of Sponsor signatories

Sponsor signatory:

[redacted]
Director,
Worldwide Clinical Development,
Rotavirus vaccine,
GSK Biologicals.

[redacted]
Deputy Director,
Clinical Development,
GlaxoSmithKline K.K.

Signature: [redacted]

Date: [redacted] 12 April 2007

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GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
ROTA-056	107625

Date: ***14 October 2009***

Concerns: Protocol Investigator Agreement

Details:

The original protocol was amended prior to submission to the investigators. Therefore Amendment #1 will be the only approval we have signed from investigators in our files.

Made by: [redacted] **Function:** CTA

(If required) Approved by: [redacted] **Approver's Signa** [redacted]

Function ***[Line Manager]*****:**_____ **Signature Date:** _____ 2009

Appendix I Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007
Co-ordinating author:	[redacted]
Rationale/background for changes: The protocol has been amended as per the request from Pharmaceutical and Medical Devices Agency (PMDA), Japan.	

Text has been deleted in the following section:
Section 5.6.3: Immunological read-outs:
Additional analysis:

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests. ~~the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.~~

It may be that any findings in the present study ~~or in other studies~~ necessitates further investigation by GSK Biologicals into the efficacy or immunogenicity of the ~~vaccine.~~ HRV vaccine and its constituents under study. ~~or further research in the disease under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.~~

~~A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.Any sample testing will be done in line with the consent of the individual subject's parents/guardians.Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.~~

CONFIDENTIAL

107625 (Rota-056)
Amendment 1

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007
Approved by: Director, Worldwide Clinical Development, Rotavirus vaccine,	[redacted] 14-05-2007 dd-mm-yyyy
Deputy Director, Clinical Development, GlaxoSmithKline K.K.	[redacted] dd-mm-yyyy

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20f83eacb735d614aa670c92c5638187 2.2 11/05/2007

CONFIDENTIAL

107625 (Rota-056)
Amendment 1

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007
Approved by: Director, Worldwide Clinical Development, Rotavirus vaccine,	[redacted] dd-mm-yyyy
Deputy Director, Clinical Development, GlaxoSmithKline K.K.	[redacted] 8 May 2007 dd-mm-yyyy

For internal use only
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20f83eacb735d614aa670c92c5638187 2.2 11/05/2007

GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
ROTA-056	107625

Date: ***14 October 2009***

Concerns: Protocol Investigator Agreement missing checksum

Details:

This File Note is to serve as documentation that the signed Japanese translated version of the Amendment 1 Protocol Investigator Agreement is missing the checksum.

Made by: [redacted] **Function:** CTA[redacted]

(If required) Approved by: [redacted] **Approver's Sign**

Function ***[Line Manager]*****:** _____ **Signature Date:** 14 Oct 2009

GlaxoSmithKline

TRANSLATION COMPLIANCE FORM

--- Please fill in all sections of this form ----

Please insure that a written confidentiality agreement is available from the third party translators, when they undertake the translations.

Protocol N°: 107625 (Rota-056).....

Protocol Title: Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants

Translation(s) requested by: [redacted] .....**Date requested: 04-Feb-08**

Translation Reference N° (if applicable): .....

Document details:

Document details:	Unique document ID*	Date of original document	Language of original document	Translated language requested
Investigator Agreement(s) (Investigator signature page)				
[redacted]		18-May-07	Japanese	English
		29-May-07	Japanese	English
		29-May-07	Japanese	English
		15-Oct-07	Japanese	English
		21-May-07	Japanese	English
		14-May-07	Japanese	English
		05-Jul-07	Japanese	English
		07-May-07	Japanese	English
		21-Sep-07	Japanese	English

GlaxoSmithKline

Hospital - National Hospital Organization (NHO)				
[redacted]	[redacted]	16-Oct-07	Japanese	English
		28-May-07	Japanese	English
		07-May-07 08-May-07	Japanese	English
		07-May-07	Japanese	English
		23-May-07	Japanese	English
		14-May-07	Japanese	English
		11-May-07	Japanese	English
		30-Oct-07	Japanese	English
		10-May-07	Japanese	English
		15-May-07	Japanese	English
		09-May-07	Japanese	English
		10-May-07	Japanese	English

*Unique document identification: for exemple version N°, date, etc.

GlaxoSmithKline

Translation details:

- Name of translator: [redacted] .....
- Function of translator: Clinical Research Department 8.....
- Address of translator: 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo...
.....[redacted].....
- Signature of translator: ...[redacted].....
- Date of translation(s): 13 / Feb / 2008
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Review details:

This translation was/ these translations were reviewed for accuracy, consistency, and clarity with the original document(s) by:

- Name of reviewer: [redacted] .....
- Function of reviewer: Clinical Research Department 8.....
- Address of reviewer: 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo...
.....
- Comments on translation(s):

(please document below any comments you may have on the translation(s) or if you feel further work on or re-work of the document(s) is necessary)

.....[redacted].....
.....[redacted].....
.....[redacted].....

- Signature of reviewer: .....[redacted].....
- Date of review: 14 / Feb / 2008
dd / mmm / yyyy

Medical review and approval (if applicable according to local regulations):

- Name and function: .....
- Signature: .....
- Date: __ / ___ / ____
dd / mmm / yyyy

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

eTrack study number and abbreviated title: 107625 (Rota-056)

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I agree to conduct properly the study in compliance with this protocol.

I agree ;

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Investigator

Date	2007/5/7
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/7
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/09
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/09
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/10
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/10
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/5/8
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/7
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/15
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/15
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/5/21
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/21
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/05/10
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/10
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/05/14
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/14
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/07
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/07
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/18
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/18
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/5/11
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/11
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/14
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/14
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/29
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/29
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/29
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/29
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

eTrack study number and abbreviated title: 107625 (Rota-056)

I agreed on Clinical Study Protocol (Version: Amendment 1, Date of approval: 27 April 2007) and Case Report Form (Date of approval: 27 April 2007), after discussion thoroughly.

I agree to conduct properly the study in compliance with this protocol.

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- To provide GSK Biologicals with an updated Curriculum Vitae and other regulatory authorities required documents.

Investigator

Date	2007/5/28
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/28
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/07/05
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/07/05
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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- To provide GSK Biologicals with an updated Curriculum Vitae and other regulatory authorities required documents.

Investigator

Date	2007/10/15
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/10/15
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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- To provide GSK Biologicals with an updated Curriculum Vitae and other regulatory authorities required documents.

Investigator

Date	2007/10/16
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/10/16
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

eTrack study number and abbreviated title: 107625 (Rota-056)

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I agree to conduct properly the study in compliance with this protocol.

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- To provide GSK Biologicals with an updated Curriculum Vitae and other regulatory authorities required documents.

Investigator

Date	2007/10/30
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/10/30
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Sample Case Report Form

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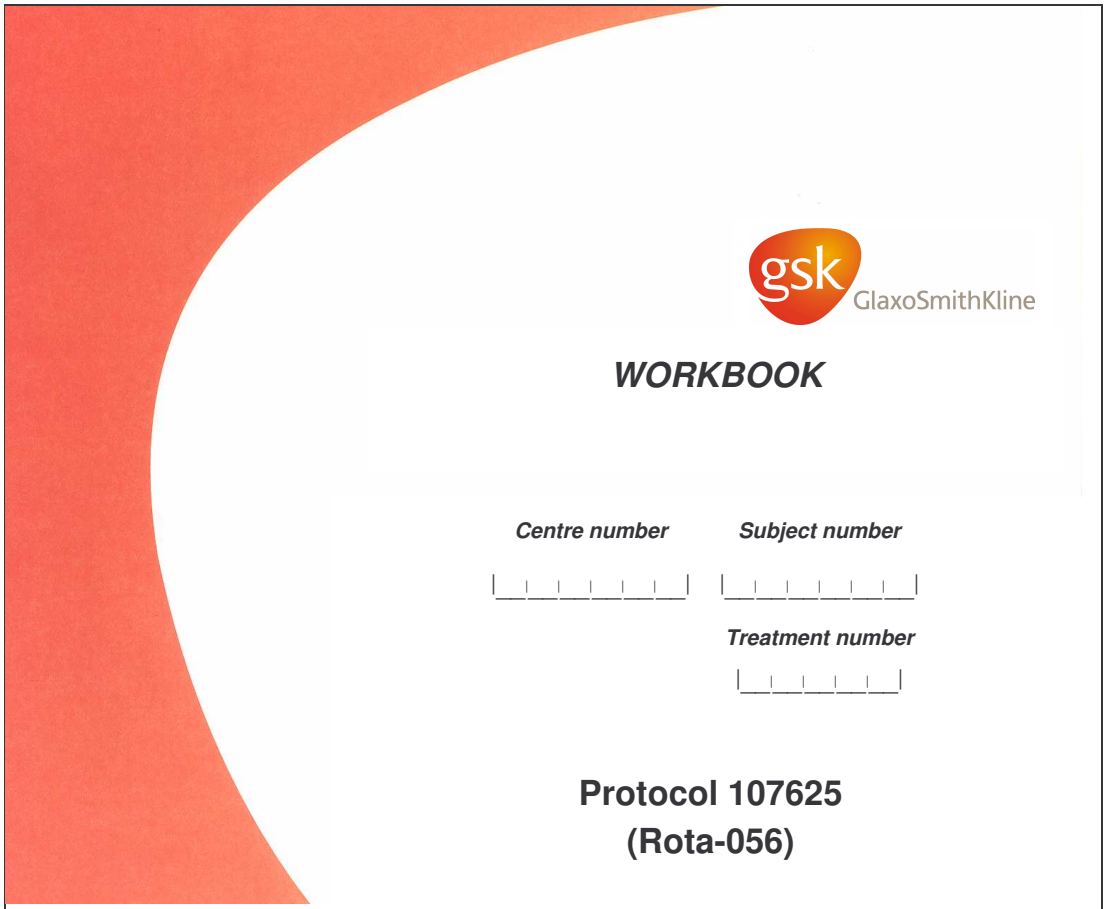

WORKBOOK

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Treatment number

|__|__|__|__|__|

Protocol 107625
(Rota-056)

A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

GlaxoSmithKline Biologicals

Rue de l'Institut 89
B – 1330 Rixensart, Belgium
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 6| = 1st January 2006
day month year

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** section(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

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

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

Vomiting

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

Diarrhea:
Three or more looser than normal stools within a day.

Gastroenteritis [GE] episode is defined as diarrhea with or without vomiting.

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ADVERSE EVENT DEFINITIONS

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: 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.
5: Fatal: AE is the cause of death (only applicable for SAE sections).

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 the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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107625 (Rota-056)

FLOW SHEET

Age	6-14 weeks			One year	Two years
Visits Timing Sampling time point	VISIT 1 Day 0 Pre-vacc	VISIT 2 Month 1	VISIT 3 Month 2 Post-vacc 2	VISIT 4	VISIT 5
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	●	●	-	-	-
Randomisation	●	-	-	-	-
Blood sampling (1 ml) for antibody determination in an immunogenicity subset *	●	-	●	-	-
Study vaccination (HRV vaccine/ Placebo)	●	●	-	-	-
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians	●	●	-	-	-
Return of reactogenicity diary card	-	○	○	-	-
Transcription of the reactogenicity diary card		●	●	-	-
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●	-	-
Record any concomitant medication/vaccination, by investigator	●	●	●	●#	●#
Recording of Gastroenteritis [GE] leading to medical intervention occurring throughout the study period	●	●	●	●	●
Contact the subject's parent/gardian to check gastroenteritis [GE] occurrence at least every two weeks	○	○	○	○	○
Collection of stool samples if subject has Gastroenteritis [GE] leading to medical intervention	●	●	●	●	●
Return of gastroenteritis [GE] diary card	-	○	○	○	○
gastroenteritis [GE] diary card transcription	-	●	●	●	●
Recording of SAEs	●	●	●	●	●
Reporting AEs leading to drop-out	●	●	●	●	●
Conclusion at Visit 4				●	
Study conclusion	-	-	-	-	●

Note: Final analysis will be done when 28 RV gastroenteritis [GE] episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV gastroenteritis [GE] leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Blood sampling will be done only from subjects in the immunogenicity subset (N = 60).

\# for concomitant medication administered for the treatment of an AE leading to drop-out/SAE.

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107625 (Rota-056)

FLOW SHEET

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed.

Intervals between study visits

Interval /Visit	Range of interval /Visit
Visit 1→Visit 2	30 - 48 days
Visit 2→Visit 3	30 - 48 days
Visit 4	1 year of age ± 15 days
Visit 5	2 years of age ± 15 days

N.B: The reference date for intervals between study visits: the first vaccination date

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VISIT 1
DAY 0
6-14 weeks of age
DOSE 1

Informed Consent has to be obtained prior to any study procedure

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107625 (Rota-056)

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.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids are allowed).

[C] Administration of immunoglobulin and/or any blood products during the study period.

[D] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine/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.

[A] Known hypersensitivity after previous administration of HRV vaccine or to any component of the vaccine.

[B] Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following AEs constitute contraindications to administration of HRV vaccine/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.

[C] Acute severe febrile illness.

[D] Diarrhoea or vomiting.

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107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**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)

Did the subject agree that her/his biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study? ☐ Yes ☐ No ☐ NA

DEMOGRAPHICS

Center number: _____

Date of Birth: ____ _____ _____ (day month year)

Gender:
[M] ☐ Male
[F] ☐ Female

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: _____

Height: ___ cm

Weight: ___ . __ kg

1.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**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) should be enrolled in the study.

[2] ☐ A male or female infant 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/guardian of the subject.

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ Born between a gestation period of 36 and 42 weeks inclusive.

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 within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ History of use of experimental rotavirus vaccine.

[8] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs prior to the first vaccine dose. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)

[9] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition determined by the investigator.

[10] ☐ History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.

[11] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1**		|__|__|__|__|__|__|

ELIGIBILITY CHECK (continued)

EXCLUSION CRITERIA

[12] ☐ A family history of congenital or hereditary immunodeficiency.

[13] ☐ Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

[14] ☐ 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. Axillary temperature <37.5°C.) Temperature greater than or equal to these cut-offs warrants deferral of the vaccination pending recovery of the subject.

[15] ☐ Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).

[16] ☐ Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

[17] ☐ Previous confirmed occurrence of RV gastroenteritis [GE].

[18] ☐ Concurrently participating in another clinical study, at any time during the study period in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number: |__|__|__|__|__|

3.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		VISIT 1		_____

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions, signs or symptoms present prior to the start of the study?

☐ 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.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1**		|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken for serology?

☐ Yes → Date if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

☐ No

☐ NA

5.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1 DOSE 1**		|__|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__| °C → Route: [A] ☐ **Axillary (mandatory)**
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Route**	**Has the study vaccine been administered according to the Protocol?**
[S] ☐ **HRV vaccine or placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral	☐ Yes ☐ No → *Please comment:* Comment: _____

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event
→ Please complete and submit **SAE** section
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete **Non-serious Adverse Event** section
→ Please specify AE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made 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** or a **Serious Adverse Event** section.

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box.

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

6.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 1**		_____

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following signs/symptoms during the solicited period?

[U] ☐ Information not available
[NA] ☐ No Vaccine administered
[N] ☐ No
[Y] ☐ 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?	Medically attended visit	HO/ER/MD
Fever [FE] ☐ No ☐ Yes → °C: [A] ☐ **Axillary (mandatory)** [O] ☐ Oral [R] ☐ Rectal	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Cough/runny nose [CO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Fussiness/ Irritability [IR] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Loss of appetite [LO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Vomiting [VO] ☐ No ☐ Yes → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Fever:
Axillary **≥ 37.5°C**
Oral ≥ 37.5°C
Rectal ≥ 38.0°C

Medically attended visit:
(see protocol for full definition)
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 1**		|__|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS (DIARRHEA) (continued)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?		Causa-lity?	Medically attended visit	
Diarrhea [DA] (*) ☐ No													
☐ Yes (**) → Number of looser than normal stools:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please complete **Gastroenteritis Episodes Leading to a Medical Intervention** section in case of diarrhea leading to medical intervention. →If not leading to medical intervention, please complete date of last symptom: |__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	☐ No ☐ Yes→	HO/ER/MD |__|__|

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Medically attended visit:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel
(see protocol for full definition)

(*) Stool sample should be collected in case of diarrhea leading to medical intervention.

Stool Collection:

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

(**) If diarrhea leading to medical intervention, please complete the following items:
Medication for diarrhea?

☐ No

☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: _____

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

8.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1**		|__|__|__|__|__|__|

FEEDING PRACTICE (*)

- ☐ only breast-fed
- ☐ only formula-fed
- ☐ only solid food
- ☐ breast-fed and formula-fed
- ☐ breast-fed and solid food
- ☐ formula fed and solid food
- ☐ breast fed, formula fed and solid food

(*) *Please tick only one box*

Time between last feeding and administration of Dose 1: |__|__| hour |__|__| min

9.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 1**		|__|__|__|__|__|__|

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination?

[U] ☐ Information not available

[NA] ☐ No vaccine administered

[N] ☐ No

[Y] ☐ Yes → Fill in the **Non-Serious Adverse Event** section or **Serious Adverse Event** section as necessary.

10.

CONFIDENTIAL

VISIT 2
MONTH 1
30-48 Days after Visit 1
DOSE 2

CONFIDENTIAL

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

GASTROENTERITIS LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 2**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for 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:
→ Please complete and submit **SAE** section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete **Non-serious Adverse Event** section.
→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

11.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention from Day 8 after Dose 1 of HRV vaccine or Placebo until Visit 2?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

12.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 2 DOSE 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__| °C → Route: [A] ☐ **Axillary (mandatory)**
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Route**	**Has the study vaccine been administered according to the Protocol?**
[S] ☐ **HRV vaccine or placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number→ |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral	☐ Yes ☐ No → *Please comment:* Comment: _____

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event
→ Please complete and submit **SAE** section
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete **Non-serious Adverse Event** section
→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made 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** or a **Serious Adverse Event** section**.**

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box**.**

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section**.**

13.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 2**		_____

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following signs/symptoms during the solicited period?

[U] ☐ Information not available
[NA] ☐ No Vaccine administered
[N] ☐ No
[Y] ☐ 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?	Medically attended visit	HO/ER/MD
Fever [FE] ☐ No ☐ Yes → °C: [A] ☐ **Axillary (mandatory)** [O] ☐ Oral [R] ☐ Rectal	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	_._ ☐ not taken	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Cough/runny nose [CO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Fussiness/ Irritability [IR] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Loss of appetite [LO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Vomiting [VO] ☐ No ☐ Yes → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Fever:
Axillary ≥ 37.5°C
Oral ≥ 37.5°C
Rectal ≥ 38.0°C

Medically attended visit:
(see protocol for full definition)
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

14.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 2**		|__|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS (DIARRHEA) (continued)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?		Causa-lity?	Medically attended visit	
Diarrhea [DA] (*) ☐ No													
☐ Yes (**) → Number of looser than normal stools:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please complete **Gastroenteritis Episodes Leading to a Medical Intervention** section in case of diarrhea leading to medical intervention. →If not leading to medical intervention, please complete date of last symptom: |__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes	☐ No ☐ Yes→	HO/ER/MD |__|__|

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Medically attended visit:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel
(see protocol for full definition)

(*) Stool sample should be collected in case of diarrhea leading to medical intervention.

Stool Collection:

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

(**) If diarrhea leading to medical intervention, please complete the following items:
Medication for diarrhea?

☐ No

☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: _____

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

15.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 2**		|__|__|__|__|__|__|

FEEDING PRACTICE (*)

- ☐ only breast-fed
- ☐ only formula-fed
- ☐ only solid food
- ☐ breast-fed and formula-fed
- ☐ breast-fed and solid food
- ☐ formula fed and solid food
- ☐ breast fed, formula fed and solid food

(*) *Please tick only one box*

Time between last feeding and administration of Dose 2: |__|__| hour |__|__| min

16.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 2**		_____

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination?

[U] ☐ Information not available

[NA] ☐ No vaccine administered

[N] ☐ No

[Y] ☐ Yes → Fill in the **Non-Serious Adverse Event** section or **Serious Adverse Event** section as necessary.

17.

CONFIDENTIAL

VISIT 3
MONTH 2

30-48 Days after Visit 2

CONFIDENTIAL

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT 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 LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 3**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 3?

☐ Yes → Please complete the next pages.

☐ No → Please complete below and skip the following pages of this visit.

☐ 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:

→ Please complete and submit **SAE** section.

→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section.

→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

18.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken for serology?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

☐ NA

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention from Day 8 after Dose 2 of HRV vaccine or Placebo until Visit 3?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

19.

CONFIDENTIAL

VISIT 4

1 year of age ± 15 Days

CONFIDENTIAL

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT 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 LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 4**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 4?

☐ Yes → Please complete the next pages.

☐ No → Please complete below and skip the following pages of this visit.

☐ 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:

→ Please complete and submit **SAE** section.

→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section.

→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

20.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 4**	___ ___ ____ (day month year)	_____

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention between Visit 3 and 4?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

21.

CONFIDENTIAL

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4

EPISODE N°: |__|__|

Treatment?
- ☐ No
- ☐ Yes → ☐ Oral rehydration
  - ☐ IV rehydration
  - ☐ Oral and IV rehydration
  - ☐ Other, please specify: ________________________

Medical intervention:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (°C) → route: ☐ Axillary (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

22.

CONFIDENTIAL

GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4 (continued)

EPISODE N°: |__|__|

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ________________________

Medical intervention:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** → route:	☐ **Axillary** (*) ☐ Oral ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4 (continued)

EPISODE N°: |__|__|

Treatment?
- ☐ No
- ☐ Yes → ☐ Oral rehydration
  - ☐ IV rehydration
  - ☐ Oral and IV rehydration
  - ☐ Other, please specify: ________________________

Medical intervention:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (°C) → route: ☐ Axillary (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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CONCOMITANT VACCINATION UP TO VISIT 4

Any vaccine not foreseen in the study protocol administered since birth up to Visit 3 is to be recorded with trade name, route of administration and date(s) of administration.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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CONCOMITANT VACCINATION UP TO VISIT 4

Have any vaccines other than the study vaccine(s) been administered as specified in the protocol up to visit 4?

☐ 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		

Route:

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

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MEDICATION
UP TO VISIT 4

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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
IN	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 31 days after each dose of study vaccine 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 or at any time during the study period up to Visit 3 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 [Axillary temperature <37.5°C (99.5°F)] 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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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MEDICATION UP TO VISIT 4

Have any medications/treatments been administered as specified in the protocol up to Visit 4?

☐ 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 UP TO VISIT 4

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NON-SERIOUS ADVERSE EVENTS UP TO VISIT 4

(Please report **serious adverse events** only on the **Serious Adverse Event (SAE)** sections).

Has any **non-serious adverse events** occurred within **one month (minimum 30 days)** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages?

☐ No

☐ Yes, please complete the following table.

AE No.	**1**	**2**
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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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107625 (Rota-056)

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NON-SERIOUS ADVERSE EVENTS UP TO VISIT 4 (continued)

AE No.	**3**	**4**
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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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CONCLUSION AT VISIT 4

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SUBJECT STATUS AT VISIT 4

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 1 and Visit 4?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 1 and Visit 4?

☐ 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 a **Serious Adverse Event** section as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 1 and Visit 4?

☐ No ☐ Yes → Specify: _____

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Protocol				Subject Number
107625				|__|__|__|__|__|__|

SUBJECT STATUS AT VISIT 4 (continued)

Is the subject withdrawn at Visit 4?

☐ No

☐ Yes → Major reason for withdrawal (tick **one** box only).

☐ [SAE] Serious adverse event:
→ Please complete and submit SAE section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete Non-serious Adverse Event section.
→ Please specify AE No. |__|__| *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: _____

→ 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: _____

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VISIT 5

2 years of age ± 15 Days

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REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT 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 LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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Protocol		Visit		Subject Number
107625		**VISIT 5**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 5?

☐ Yes → Please complete the next pages.

☐ No → Please complete below and skip the following pages of this visit.

☐ 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:

→ Please complete and submit **SAE** section.

→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section.

→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 5**	___ ___ ____ (day / month / year)	_____

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention between Visit 4 and 5?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION VISIT 4 TO 5

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION BETWEEN VISIT 4 AND VISIT 5

EPISODE N°: \|__\|__\|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ______________________________

Medical intervention: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical intervention: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|

Stool collection date and time: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
day month year hours min

Stool collection date and time: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
day month year hours min

Date (day month year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (°C) → route: ☐ Axillary (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION BETWEEN VISIT 4 AND VISIT 5 (continued)

EPISODE N°: |__|__|

Treatment?
- ☐ No
- ☐ Yes → ☐ Oral rehydration
  - ☐ IV rehydration
  - ☐ Oral and IV rehydration
  - ☐ Other, please specify: ________________________

Medical intervention:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (°C) → route: ☐ Axillary (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION BETWEEN VISIT 4 AND VISIT 5 (continued)

EPISODE N°: |__|__|

Treatment?
- ☐ No
- ☐ Yes → ☐ Oral rehydration
  - ☐ IV rehydration
  - ☐ Oral and IV rehydration
  - ☐ Other, please specify: _________________________

Medical intervention:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (℃) → route:** ☐ Axillary (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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CONCOMITANT VACCINATION

VISIT 4 TO 5

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Have any vaccines other than the study vaccine(s) been administered between Visit 4 and 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		

Route:			
ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

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MEDICATION
VISIT 4 TO 5

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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

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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments been administered between Visit 4 and 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					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

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NON-SERIOUS ADVERSE EVENTS VISIT 4 TO 5

All AEs leading to subject withdrawal or drop-out must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report **serious adverse events** only on the **Serious Adverse Event (SAE)** sections).

Has any **non-serious adverse events** occurred between Visit 4 and 5 leading to drop-out?

☐ No

☐ Yes, please complete the following table.

AE No.	**51**	**52**
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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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GlaxoSmithKline

107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

AE No.	**53**	**54**
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|__|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 4 and 5?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 4 and 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 a **Serious Adverse Event** section as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 4 and 5?

☐ No ☐ Yes → Specify: _____

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|__|

STUDY CONCLUSION (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** section.
  - → Please specify SAE No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| *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: _____

→ 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: _____

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GlaxoSmithKline

107625 (Rota-056)

Protocol	Centre	
107625	|__|__|__|__|__|__|__|	

USE OF HUMAN SAMPLES BY GSK

In addition to the use of samples for the tests described in the protocol, samples might be used for other resarch by GSK (see protocol). Please tick what is also covered by the subject Informed Consent form of your center.

[2] ☐ **Quality Assurance of tests described in the protocol**

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in the protocol as well as making sure that new tests are comparable to previous methods and work reliably.

[3a] ☐ **Further investigation by GSK Biologicals into the ability of HRV vaccine to protect people if any findings from related studies require it and further research in Rotavirus. These investigations excludes genetics and HIV testing.**

[3b] ☐ **Further investigation by GSK Biologicals into the ability of HRV vaccine to protect people if any findings from related studies require it and further research in Rotavirus. These investigations excludes genetic and HIV testing. Investigator will always ask in advance the permission of the independent Ethics Committee/Institutional Review Board linked to the institution where this research is performed.**

[4] ☐ **Further research by GSK Biologicals that is NOT RELATED to HRV vaccine or the Rotavirus done on an anonymous basis (meaning that any identification linking the subject to the sample is destroyed). This research excludes genetic and HIV testing and does not affect subject participation in the study.**

Please tick below box if a 15 years GSK storage period is covered by the subject's Informed Consent form of your center.

☐ **At least 15 years storage period by GSK Biologicals**

☐ **Other, specify:**_____

ICF Effective date: |__|__| |__|__|__| |__|__|__|__|
day month year

! Complete and submit a new form for each change during the study.

INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

1.

Protocol	DIARY CARD	DOSE 1	Subject number
107625 (Rota-056)	SOLICITED SYMPTOMS		_____

SOLICITED GENERAL SYMPTOMS
I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting, Diarrhea

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 axillary temperature every day. Please take temperature in the evening. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose	**Irritability / fussiness:**	**Loss of appetite:**
0:Normal	**0**:Behavior as usual	**0**:Normal
1:Cough/runny nose which is easily tolerated	**1**:Crying more than usual / no effect on normal activity	**1**:Eating less than usual / no effect on normal activity
2:Cough/runny nose which interferes with daily activity	**2**:Crying more than usual / interferes with normal activity	**2**:Eating less than usual / interferes with normal activity
3:Cough/runny nose which prevents daily activity	**3**:Crying that cannot be comforted / prevents normal activity	**3**:Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents > 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

SOLICITED SYMPTOMS	Day0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms Year month day
Date□	__/__	__/__	__/__	__/__	__/__	__/__	__/__	__/__		
Axillary Temperature → °C:	__._	__._	__._	__._	__._	__._	__._	__._	☐ No ☐ Yes →	200__|__|__|
Cough/runny nose → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Whimpering (or Irritability/ Fussiness) → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Loss of appetite → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Vomiting → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Diarrhea (*) → number of looser than normal stools:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	if ongoing after day 7 please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET
Stools samples taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

Stool collection date: __\|__\|___\|____\|_____\| hour: __\| min: __\|
Stool collection date: __\|__\|___\|____\|_____\| hour: __\| min: __\|

☐MEDICATION FOR DIARRHEA☐ ☐MEDICAL ATTENTION☐

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: _____
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200__\|__\|__\|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
Diary Card Template CRF Version 12.4, May 14 2007

PLEASE INFORM: ……..…… ☎: ……..……

Protocol	DIARY CARD	DOSE 2	Subject number
107625 (Rota-056)	SOLICITED SYMPTOMS		_____

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting, Diarrhea

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 axillary temperature every day. Please take temperature in the evening. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose	**Irritability / fussiness:**	**Loss of appetite:**
0:Normal	**0**:Behavior as usual	**0**:Normal
1:Cough/runny nose which is easily tolerated	**1**:Crying more than usual / no effect on normal activity	**1**:Eating less than usual / no effect on normal activity
2:Cough/runny nose which interferes with daily activity	**2**:Crying more than usual / interferes with normal activity	**2**:Eating less than usual / interferes with normal activity
3:Cough/runny nose which prevents daily activity	**3**:Crying that cannot be comforted / prevents normal activity	**3**:Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents > 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

SOLICITED SYMPTOMS	Day0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms Year month day
Date□	__/__	__/__	__/__	__/__	__/__	__/__	__/__	__/__		
Axillary Temperature → °C:	__._	__._	__._	__._	__._	__._	__._	__._	☐ No ☐ Yes →	200__|__|__|
Cough/runny nose → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Whimpering (or Irritability/ Fussiness) → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Loss of appetite → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Vomiting → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	200__|__|__|
Diarrhea (*) → number of looser than normal stools:	__	__	__	__	__	__	__	__	☐ No ☐ Yes →	**if ongoing after day 7 please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

Stool collection date: __\|__\|___\|____\|_____\| hour: __\| min: __\|
Stool collection date: __\|__\|___\|____\|_____\| hour: __\| min: __\|

☐MEDICATION FOR DIARRHEA☐ **☐MEDICAL ATTENTION☐**

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: _____
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200__\|__\|__\|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

Diary Card Template CRF Version 12.4, May 14 2007

PLEASE INFORM: ……..…… ☎: ……..……

Protocol	DIARY CARD		Subject number
107625 (Rota-056)	FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 7	DOSE 1	|__|__|__|__|__|__|__|

SOLICITED DIARRHEA SYMPTOM If the symptom continues After 7 days

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 axillary temperature every day. Please take temperature in the evening. 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 continue after 7 day, please continue to assess the following Symptoms until the end of the diarrhea.
(*) If not already collected during the period from D0-D7, please collect stools samples in case of diarrhea leading to medical intervention.

SOLICITED DIARRHEA SYMPTOMS	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__
Axillary Temperature → °C:	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _
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

Stool collection date: |__|__|__|__|__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__|__|__|__|__|__|__| hour: |__|__| min: |__|__|

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |**200**|__||__|__|__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ……..…… ☎: ……..……

Protocol	DIARY CARD	DOSE 2	Subject number
107625 (Rota-056)	FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 7		|__|__|__|__|__|__|__|

SOLICITED DIARRHEA SYMPTOM If the symptom continues After 7 days

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 axillary temperature every day. Please take temperature in the evening. 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 continue after 7 day, please continue to assess the following Symptoms until the end of the diarrhea.
(*)If not already collected during the period from D0-D7, please collect stools samples in case of diarrhea leading to medical intervention.

SOLICITED DIARRHEA SYMPTOMS	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__
Axillary Temperature → °C:	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
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

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |200|__||__|__| |__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 1	Subject number
107625 (Rota-056)	OTHER GENERAL SYMPTOMS AND MEDICATION		|__|__|__|__|__|__|__|

UNSOLICITED SYMPTOMS Up to 30 day from vaccination day

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).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis Symptoms) Please give detail below	Intensity 1.Mild 2Moderate 3.Severe	Start date Year month day	End date or check box if continuing Year month day	Continuing
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐

MEDICATION	Please fill in below if any medication has been taken from the vaccination day till 30 days post vaccination					
Trade/Generic name (excluding rehydration)	Reason	Route	Total Daily Dose	Start date Year month day	End date or check box if continuing Year month day	Continuing
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐

☐ **MEDICAL ATTENTION** ☐

- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200|_||_|_||_|_|

YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

PLEASE INFORM: ………………………………………… ☎: ……………………………………………………………

Protocol	**DIARY CARD**	DOSE 2	Subject number
107625 (Rota-056)	OTHER GENERAL SYMPTOMS AND MEDICATION		|__|__|__|__|__|__|

UNSOLICITED SYMPTOMS □Up to 30 day from vaccination day□

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).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis Symptoms) Please give detail below	Intensity 1.Mild 2Moderate 3.Severe	Start date Year month day	End date or check box if continuing Year month day	Continuing
	|__|	200|__||__|__||__|__|	200|__||__|__||__|__|	☐
	|__|	200|__||__|__||__|__|	200|__||__|__||__|__|	☐
	|__|	200|__||__|__||__|__|	200|__||__|__||__|__|	☐
	|__|	200|__||__|__||__|__|	200|__||__|__||__|__|	☐
	|__|	200|__||__|__||__|__|	200|__||__|__||__|__|	☐
	|__|	200|__||__|__||__|__|	200|__||__|__||__|__|	☐

MEDICATION	Please fill in below if any medication has been taken taken from the vaccination day till 30 days post vaccination					
Trade/Generic name (excluding rehydration)	Reason	Route	Total Daily Dose	Start date Year month day	End date or check box if continuing Year month day	Continuing
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐
				200|__||__|__||__|__|	200|__||__|__||__|__|	☐

☐**MEDICAL ATTENTION**☐
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200\|__\|\|__\|__\|\|__\|__\|

YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

PLEASE INFORM: ………………………………………… ☎: ……………………………………………………………

Diary Card Template CRF Version 12.4, May 14 2007

Protocol	DIARY CARD	DOSE 1	Subject number
107625 (Rota-056)	GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION		|__|__|__|__|__|__|

GASTROENTERITIS EPISODE□Diarrhea which appears newly after 7 day post vaccination□

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 axillary temperature every day. Please take temperature in the evening. 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 leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

EPISODE No.:_____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Axillary temperature → °C:	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
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

Stool collection date: |_|_| |_|_|_| |_|_|_|_| hour: |_|_| min: |_|_|
Stool collection date: |_|_| |_|_|_| |_|_|_|_| hour: |_|_| min: |_|_|

☐MEDICATION FOR DIARRHEA☐

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: _____

☐MEDICAL ATTENTION☐

- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |200|__||__|__|__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ……..…… ☎: ……..……

Protocol	DIARY CARD	DOSE 2	Subject number
107625 (Rota-056)	GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION		|__|__|__|__|__|__|

GASTROENTERITIS EPISODE: Diarrhea which appears newly after 7 day

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 axillary temperature every day. Please take temperature in the evening. 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 leading to medical intervention.
Please record the following "MEDICATION FOR DIARRHEA" and "MEDICAL ATTENTION".

EPISODE No.:_____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C:	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
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

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

☐MEDICATION FOR DIARRHEA☐

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: _____

☐MEDICAL ATTENTION☐

- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |**200**|__||__|__|__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ……..…… ☎: ……..……

List of Independent Ethics Committees /Institutional Review Boards

Centre Number(s) *	Ethics Review Body	Location
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted] Dr. [redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]

* GSK Biologicals assigned centre number, check with GSM/Study Manager

Representative written information for patient and sample consent forms

Protocol No.: 107625 (Rota-056)
Version 2

Study title: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV.
Company name: GlaxoSmithKline Biologicals KK

Subject identification: _____

HRV Vaccine

Informed Consent Form (Sample)

Written explanation and consent statement for the parent(s)/guardians of the subjects requested to participate in the clinical study of HRV vaccine

Date of Preparation: March 30, 2007

Date of Revision: May 07, 2007

To Parent(s)/Guardians

Human Rotavirus (HRV) vaccine is a vaccine under development by GlaxoSmithKline K.K. It is expected to prevent infection with rotavirus which causes rotavirus gastroenteritis. It has been already approved in more than 60 countries in the world and has been administered to more than one million infants and young children.

The most common cause of diarrhoeal illness in infants and young children is a virus called "rotavirus", which causes gastroenteritis called "rotavirus gastroenteritis (GE)", and most of the children between 6 and 24 months of age are affected.

The most frequently observed symptom of rotavirus disease (or gastroenteritis) is diarrhoea ("white watery stool" such as the water after washing rice) associated with pain and vomiting. This white watery stools may occur for up to ten stools per day and may last from 3 to 9 days. Other symptoms such as fever and abdominal pain may also occur. Diarrhoea 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 infants and young children in developed countries and is a leading cause of death in poorer countries.

As of 15 July 2005, around 89,240 infants have been enrolled in clinical trials with GSK Biologicals' freeze-dried HRV Vaccine. It was confirmed from the study results that "antibodies" (substances in the blood that fight rotavirus infections) were produced in infants and young children by administration of the HRV Vaccine (oral ingestion of the vaccine). Administration of the HRV Vaccine also decreased the occurrence of rotavirus gastroenteritis during the two years after vaccination in Finland and Latin America. The HRV Vaccine also decreases occurrence of severe rotavirus diarrhea in infants and reduces hospitalisation due to rotavirus disease.

Explanation of study participation is to be originally given to a person who is going to participate in the study but the explanation here is to be given to parent(s)/guardians instead of subjects because this study is performed in infants and young children.

Please take time to think before you decide to have your child/ward participate in this study. Immediate reply is not necessary. Please do not hesitate to ask any question. You may also want to bring this document back home and discuss with your family, friends, relatives, etc. Once you read these explanatory documents and you decide to have your child/ward participate in the study, you will be asked to fill in the form (for informed consent) on the last page with dates and your signature or seal.

However, please inform us if your child/ward participated in other study within the past 30 days or have plans to do so.

Please do not leak the information relating to clinical trial to other people because the information and documents that you get with a clinical trial are the confidential information that GSK owns. But it shall not be limited that you talk with your friend and family about this clinical trial as well as doctor to consult about your health control.

1. What is a clinical study?

Currently, various kinds of vaccines and drugs are used and they all have been approved by the Ministry of Health, Labour and Welfare for their use. In order to obtain approval, the results of studies investigating "whether the drug or vaccine has protective effect", "whether the drug or

vaccine is effective", "whether the drug or vaccine is safe", "whether the drug or vaccine is superior to the currently used drugs or vaccines" should be submitted for examination. Among these studies (researches), those conducted in humans are called "Clinical Study". Vaccines or drugs examined in clinical studies are called "Study Vaccine" or "Study Drug".

In the process of development, the effectiveness and safety of a vaccine or drug are first investigated in animals, and then the safety in healthy humans is evaluated by investigating the amount of the drug in blood and urine, etc. After that, some studies are necessary; the vaccine is used in healthy humans to examine whether it prevents the target disease and its safety or the drug is used actually in patients to examine whether the drug is safe and effective.

Clinical studies are therefore necessary steps to create better vaccines to treat the patients to prevent diseases or suffering from diseases.

The procedures and contents of a clinical study are discussed to protect the participants' rights by the Institutional Review Board and the study is started after the approval is obtained. This clinical study has been already discussed and approved in such a manner by the Institutional Review Board.

Institutional Review Board (IRB)

The Institutional Review Board below reviewed and discussed the appropriateness of performing this clinical study.

Type and address of IRB	Contents of review/discussion
IRB of OO Hospital	*Review of the study plan from scientific and ethical aspects*
Name of a technical IRB	*Review of technical items related to OO*
Name of a third party IRB	*Review of the study plan from scientific and ethical aspects*

Please ask when you have a question about IRB (about management and activity of IRB)

2. Why is this clinical study performed?

Since there is no effective treatment for rotavirus gastroenteritis and only the symptomatic therapy (treatment for making the symptom milder) is available, vaccination is the best way to prevent rotavirus gastroenteritis.

GlaxoSmithKline K.K. has developed a new rotavirus vaccine called "HRV Vaccine" based on human rotavirus. The HRV Vaccine is a weakened live vaccine (rotavirus was weakened in toxicity and processed to produce only the antibodies for rotavirus). When a child is vaccinated, the child is expected to develop antibodies (substance in the blood that fights infection) so that only a mild infection with few or no symptoms manifests even if he/she is infected with rotavirus.

This clinical study is performed to investigate the protective effect of the HRV Vaccine against rotavirus gastroenteritis and safety in Japanese infants.

3. What does this study involve?

The study is planned to involve a total of 765 Japanese infants aged 6 to 14 weeks (42 to 104 days after birth). Either of the two types of vaccine, HRV Vaccine and Placebo (product that looks like the real vaccine, but does not contain any active ingredient i.e. virus), will be administered orally. The HRV Vaccine and Placebo are assigned at a ratio of 2:1 (the HRV Vaccine will be given with a probability of 2 out of 3 infants and Placebo to 1 out of 3 infants). Whether your child/ward is assigned to the HRV Vaccine Group or Placebo Group is not known to the physician in charge or you so that the protective effect and side effects of the HRV Vaccine can be objectively evaluated.

Subjects in the HRV Vaccine Group and the Placebo Group will receive two oral doses (the study vaccine is taken orally) of the HRV Vaccine or Placebo at an interval of one month.

All infants participating in this study can receive routine childhood vaccines like DTPa (diphtheria, tetanus toxoids, and pertusis) and HBV (hepatitis B virus vaccine). Other vaccines can be administered according to the Japanese immunisation schedule.

There are a total of five scheduled visits during the study period (until your child/ward becomes 2 years old). You will determine the dates and procedures of visits by consulting the sub-investigator or study nurse so that they do not fall outside the predetermined schedule.

<In order to be included in the study, the following requirements must be met>

- Parent(s)/guardian of the child/ward have given written informed consent.
- The child/ward is aged between 6 and 14 weeks at the time of first vaccination and was born between a gestation period of 36 and 42 weeks inclusive (either boy or girl).
- The child/ward has been confirmed to be healthy before the start of the study by medical history and examination
- Parent(s)/guardians must comply with the requirements of schedule and notes on this Informed Consent Form.

<**Actual procedures and contents of this study are summarised below**>

- Your child/ward will make a total of 5 visits as follows: first vaccination (Visit 1), 1 month after the first vaccination, 2 months after the first vaccination, at the age of 1 year, and at the age of 2 years. During the two years, you will be contacted periodically (at least every 2 weeks) by e-mail, by telephone or by other means to ask the health state of your child/ward.
- Your child/ward will be given a total of two oral vaccinations at the first vaccination (Visit 1) and 1 month later. After each vaccination, you will stay at the study centre for at least 30 minutes to make sure your child/ward is feeling okay before going home.
- Before administration of the vaccine, your child/ward's body temperature will be measured.
- "Diary Card (Solicited symptoms)" "Diary Card (Follow-up of solicited diarrhoea symptoms ongoing after Day 7)", "Diary Card (Other general symptoms and medication)" and "Diary Card (Gastroenteritis episodes)" will be provided to you to record the health state of your child/ward after administration of the study vaccine. Please record the health state of your child/ward on these diary cards and bring them at the next visit.

Diary Card (Solicited symptoms)

Any specific symptom (those listed below) which might occur on the day of vaccination and for the following 7 days (8 days in total):

- Fever (body temperature), fussiness/irritability, loss of appetite, cough /runny nose, vomiting, diarrhoea

Note: If diarrhoea continues after Day 7, please record the end of the symptoms in "Diary Card (Follow-up of solicited diarrhoea symptoms ongoing after Day 7)"

Diary Card (Other general symptoms and medication)

Any symptom (listed below) which might occur on the day of vaccination and during the following 30 days (in total 31 days after the vaccination)

- All symptoms (all unusual symptoms excluding those already recorded in the Diary card for solicited symptoms.

Diary Card (Gastroenteritis Episodes)

From 8 days after vaccination to the end of study: Occurrence of Diarrhoea leading to medical intervention for your child/ward during this period should be recorded.

- If you agree that your child is part of the subset of 60 subjects who will give blood sample, 1 ml (about one teaspoonful) of blood will be collected from your child/ward at the scheduled two visits (at the first vaccination and 2 month later). The purpose of the blood sample collection is to evaluate the immune responses (i.e. production of antibodies) to the HRV Vaccine that your child/ward may receive. Blood samples will not be used for any other purpose than investigation of the HRV Vaccine.
- At each visit, a physical examination will be performed and the feeding practices of your child will be recorded.
- 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.
  - Intussusception: Serious disease with telescoping of one portion of the intestine into another: symptoms consistent with intussusception are, severe colicky abdominal pain (the child may cry hard by pulling his/her legs up to the trunk), quite normal activities between episodes, persistent vomiting, strawberry jam-like stools, abdominal bloating (abdominal distension), and high fever (up to 41°C in some cases).
- You should also collect a stool sample from your child/ward during occurrence of diarrhoea (Passage of three or more looser than normal stools within a day) leading to medical intervention. Stool samples should be collected in a container provided by the institution as soon as possible (not later than 7 days after the occurrence of diarrhoea (diaper with stool is acceptable if it is difficult to collect a stool sample). If diarrhoea recurs after 5 days after disappearance of the symptom, it should be considered as a separate episode and you should take a stool sample again.
- You will be asked to report the following information about your child/ward:
  - Use of any medication or other vaccine/placebo during the study period.

- Symptoms and diagnosis, if your child/ward receives examination/treatment at other department or medical institution

- Note: You should contact the physician in charge or other study nurse immediately should your child/ward have any signs or symptoms you think may be serious, or if your child/ward is hospitalised during the study period.

  - **List of investigation items during the study –**

Timing of Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	6-14 weeks after birth	1 month later	2 month later	At the age of 1 year	At the age of 2 years
Medical examination	●	●	●	●	●
Body temperature before vaccination	●	●			
Vaccination	●	●			
Submission/return of Diary Card (Solicited symptoms)	●	●	●		
Diary Card (Follow-up of solicited diarrhoea symptoms ongoing after Day 7)	●	●	●		
Submission/return of Diary Card (Other general symptoms and medication)	●	●	●		
Collection of GE stool samples*	●	●	●	●	●
Submission/return of Daily Card (Gastroenteritis episodes)	●	●	●	●	●
Blood collection**	●		●		

* Stools samples are to collected it when your child/ward has diarrhoea (Passage of three or more looser than normal stools within a day) leading to medical intervention

**Blood samples will be taken from your child/ward only if you agree to be part of the immuno subset.

4. How long is the duration of participation in the study?

The participation of your child/ward in the study is about 22 months, starting from the first dose of HRV vaccine/Placebo until your child/ward becomes 2 years of age.

5. How many other subjects are there in the study?

This study will involve a total of approximately 765 male or female infants in multiple centres in Japan.

6. Does your child/ward have to participate in the study? Does your child/ward have to stay in the study?

You may refuse your child's/ward's participation in this study, or once in the study you may decide to discontinue participation at any time. Your decision to not let your child/ward take part in the study or to stop participating in the study will not affect your child's/ward's current or future medical care, or any benefits to which your child/ward may otherwise be entitled. However, the sponsor of this study, GlaxoSmithKline K.K., will store and use the information obtained in this study without disposing it even if your child/ward discontinues participation in the study.

Study participation may be discontinued in the cases described below. In these cases, you will be informed of the reason for discontinuation.

- When the parent(s)/guardian wishes study discontinuation.

- When it is found out that your child/ward should not participate in the study after the study initiation.
- When the study has reached the required number of subjects.
- When your child's/ward's participation in the study is judged to be difficult due to side effects.
- When discontinuation of your participation is judged necessary by the physician in charge upon the medical judgment.
- When your child/ward changes his hospital and cannot make a hospital visit any longer.
- When the study itself is discontinued due to the sponsor's own reason.

When new information that may affect your willingness to let your child/ward stay in the study becomes available, we will tell you as soon as possible about the information. You will be asked to determine whether or not to continue participation in the study.

7. What are the foreseeable benefits for taking part in the study? What are the expected side effects?

<Foreseeable benefits>

When your child/ward is vaccinated with the HRV Vaccine, there may not be gastroenteritis symptoms such as diarrhoea and vomiting or the symptoms may be mild even if he/she is infected with rotavirus and your child/ward will be protected against rotavirus gastroenteritis. When a Placebo is vaccinated, there is no foreseeable benefit.

<Side effects observed so far>

The HRV Vaccine has been studied in overseas research studies in which approximately 40,200 infants and young children received the said vaccine. Most of the adverse experiences observed with the HRV Vaccine were mild (Table below) and the incidence of the adverse experiences caused by the HRV Vaccine was similar to that of placebo.

≥ 10%	≥ 0.1% and < 1%	≥ 0.01% and < 0.1%	< 0.01%
Irritability and loss of appetite	Fever, fatigue, diarrhoea, vomiting, flatulence (gas), abdominal pain, and regurgitation of food	Crying, sleep disorder, somnolence (sleeping longer than usual, or always looking drowsy), constipation,	upper respiratory tract infection, hoarseness, rhinorrhoea, dermatitis, rash, and muscle cramp (twitching of the muscles)

It was reported in an overseas study that the rate of occurrence of intussusception was increased with a different HRV vaccine (other than GSK Biologicals vaccine) which was used in the United States in 1998. In a large safety trial (involving about 63,200 infants and young children), the results have shown that the HRV Vaccine being tested in this study does not increase the possibility of causing intussusception compared with placebo (HRV Vaccine is not likely to cause intussusception). As with any experimental vaccine, unexpected serious adverse experiences, including allergic reactions to the vaccine, may occur. All the medical equipment necessary to treat any serious reactions to the study vaccine will be available at the investigation site.

If your child is part of the immunogenicity subset, there may be momentary, mild discomfort and bruising of the skin where the needle is inserted to draw blood. The amount of blood to be taken is

so small that it will not cause any general symptoms or anaemia (a condition with insufficient red blood cells).

8. Are there alternative products or treatment?

There is no licensed rotavirus vaccine or drug currently available in Japan. Gastroenteritis caused by rotavirus is treated with oral rehydration solutions to prevent dehydration due to diarrhoea. Intravenous fluid replacement may be necessary when it is difficult to orally take water or dehydration becomes worse even if a patient can take water. Usually no treatment is performed to improve vomiting or diarrhoea caused by rotavirus gastroenteritis.

9. Who will make payment for participation in the study?

There will be no charge for study-related doctor visits, examinations and laboratory tests.

When you allow your child/ward to participate in this study, _____ yen will be paid to you for each visit to reimburse the cost of traveling to and from study visits and communication costs related to the study.

10. Who should you contact to answer any questions on the study?

If you have any questions concerning this study, please contact the physician in charge (investigator, subinvestigator) or other study nurse at the telephone number below.

Hospital:

		Name (affiliation/title)	Contact (telephone number)
Physicians in charge	Investigator	(Director, pediatrics) OO OO (Chief physician, pediatrics)	OO-OOOO-OOOO
	Sub-investigator	OO OO (physician, pediatrics) OO OO (physician, pediatrics) OO OO (physician, pediatrics)	
Study nurse		OO OO (study coordinator) OO OO (study coordinator) OO OO (study coordinator)	

11. In the event if your child/ward is injured in the study, what compensation will be available?

If you believe your child/ward has sustained a research-related injury such as side effects during or after completion of the study, you should contact the physician in charge or other study nurse immediately. Appropriate examination and treatment will be given. The expenses required for treatment and other damages will be appropriately compensated if the cause of injury is related to this study. However, compensation may be reduced or no compensation will be made if the injury is caused by your failure to observe the instructions of the physician in charge or your false report.

12. Who will have access to medical and personal information about your child/ward that is collected in this study? In that case, is the personal information protected?

If you decide to allow your child/ward to 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 staff who see this information at the site will keep it confidential.

The study site will also transfer to GSK some of the information it collects, in a coded form. The information transferred will not include your child/ward's name, initials, address, or other direct identifiers. It will be assigned a code number that only the site can connect back to your child's/ward's name.

Your permission to the study doctor and staff to use this information or share it with GSK and others as described below for the study doesn't automatically end at a particular time.

Medical information about your child/ward may be produced as part of the research or study procedures. If at the time of the study, this information is known to be relevant to your child's/ward's medical care it will be given to the study doctor who will be encouraged to share it with you or your child's/ward's doctor. While your child/ward is in the study, however, the study site will not share certain new medical information about your child/ward that is created as part of the study (such as whether or not your child/ward is getting study drug, or the results of certain tests) unless the study doctor decides it is medically important to do so. This is done to stop the study results from being distorted. Once the study is over, your child/ward will be given access to medical information about your child/ward that you are entitled to see. You will be told if any of this medical information requires confirmation using a clinical test. This is important because some research results are for research purposes and may have only limited relevance for clinical diagnosis or treatment. At any time, you may ask your study doctor to let you see your child's/ward's personal information, e.g. name and address and to correct it if necessary.

13. What will GlaxoSmithKline do with the information it gets?

GSK may use the information obtained in the clinical study (the subject number will be used in place of your child's/ward's name) in the following manner:

- By placing it under strict storage. The information will be analysed to find out what this study is telling us.

- By sharing it with regulatory authorities that approve new medicines, or with groups that check that research is done properly
- By publishing the results of the study. The study results obtained from your child/ward may be used for approval application or published in science journals. In such cases, your child's/ward's name will be replaced by a symbol or number so that your child's/ward's personal information can be secured.
- By sharing it as part of research with other companies or universities and with other GlaxoSmithKline offices in this country and in other countries for the purpose of further understanding or developing this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- By using it to plan new studies or other types of research or other medical purposes related to the development of the vaccine.

14. What will happen to the stool and blood samples obtained in this study?

The samples of diarrhoeal stool or blood (only when prior informed consent is obtained to sample the blood of your child/ward) will be collected in this study to evaluate the immunogenicity and efficacy of the study vaccine. The subject number instead of the name of your child/ward will be attached to the collected samples to protect the privacy of your child/ward and the collected samples will be transferred to GlaxoSmithKline K.K. or to other testing institutions working with GlaxoSmithKline K.K. and then tested there.

By agreeing to take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:

- Testing to measure the immune response (e.g. amount of antibodies) and efficacy of the vaccine your child/ward received during the Study.
- Testing to assure that the results from your child's/ward's sample are of good quality, for improvements of those tests.
- Collected samples will be stored for up to 15 years.

15. How is GlaxoSmithKline involved?

The study is conducted upon GSK request. The institution is paid to conduct this research study by GSK.

16. Is there any requirement to be observed by participating in the study?

Please make sure to observe the items below because they are necessary to maintain the health of your child/ward during the study -

- Please let the physician in charge or other study nurse know immediately if you feel something different in your child's/ward's body or experience any unusual events in daily life such as fracture and fall which are generally considered unlikely to be related to the study after stating the study vaccine.
- Please let the physician in charge or other study nurse know as soon as possible when you want to discontinue your child's/ward's participation in the study after starting the study vaccine.

- In case that you take your child/ward to visit other department or physician after starting the study vaccine, please let the physician know your child's/ward's participation in the study. Also, please let the physician in charge know such visit.
- Please contact the physician in charge or other study nurse when your child/ward occurrence of diarrhoea (Passage of three or more looser than normal stools within a day) leading to medical intervention.
- Please make accurate entries on the Diary Card you received according to the instructions of the physician in charge or other study nurse because they are important information for finding out the reaction to the study vaccine.
- Please contact us in advance if you cannot make a visit on the day informed by the physician in charge or other study nurse.

Please put your signature on next page if you agree on your child's/ward's participation in the study after reading the descriptions on this explanatory document.

Protocol No.: 107625 (Rota-056)
Version 2

Subject identification:_____

Consent statement

A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV.

I, (Printed name of Subject's parents/guardians)

- confirm that I have read the written information (or have had the information read to me) for study 107625 (Rota-056) dated 07 May 2007, total of 13 pages, and the study procedures have been explained to me by study staff during the consent process for this study.
- 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 taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my child's/ward's primary health care physician will be notified of my child's/ward's participation in this study. **Yes** **No**

I agree to be part of the blood sample subset: **Yes** **No**

I agree to let my child/ward to take part in this study.

I received the copy of this consent statement.

Signature of Legal Representative _____ **Date:** _____

Relationship _____

Signature of investigator _____ **Date:** _____

Date of explanation given by Investigator

Signature of study nurse _____ **Date:** _____

Date of explanation given by study nurse

List of investigators and other important participants in the study, contact information and number and distribution of subjects

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Investigator’s name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number
[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]

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number
[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]

* GSK Biologicals' assigned center number
As of 30Jun2009

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

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 III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study: 107625 (Rota-056) Development Phase: III

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: _____

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Global Clinical Research and Development
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Study: 107625 (Rota-056) Development Phase: III

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] M.B.B.S

Title of Sponsor Signatory: Director, Rotavirus vaccines
Global Clinical Research and Development
GlaxoSmithKline Biologicals

Signature: _____

Date: _____

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Study: 107625 (Rota-056) Development Phase: III

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:	Dr. [redacted]
Title of Sponsor Signatory:	Deputy Director, Clinical Development, GlaxoSmithKline K.K.
Signature:	_____
Date:	_____

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Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable.

Randomisation List

As the study is still ongoing, the blinding will be maintained for the whole study period. The randomisation list will be provided only after complete archival of the database after the completion of the study.

Audit Certificates

Audit Certificate

During the conduct and reporting of this study, the following independent GCP* audit was performed in Japan by GlaxoSmithKline K.K. Regulatory Compliance Department.

Clinical study drug code: 444563

Protocol number: 107625(Rota-056)

Study title: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study period: 19th June 2007 (FSFV) – ongoing

Audit Type	Audit date	Issue date of audit report	Referred SOP
Protocol (Informed Consent Form)	4th-10th Apr. 2007	9th May 2007	SOP/GSK/CC/003/03
Investigator site			
[redacted]			
In-house audit	6thAug.-8thSep.2008	28th Oct. 2008	SOP/GSK/RCD/005/01
On-site audit	9th - 10th Sep. 2008		
Documents/records audit	8th Sep. 2008		

Name [redacted] Date: Sept. 8, 2009

[redacted]

Department Manager,
Regulatory Compliance Department
Development and Medical Affairs Division
GlaxoSmithKline K.K.

* Ministry of Health and Welfare Ordinance No.28, 1997, and its amendments.

AUDIT CERTIFICATE

Study Number: 107625

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/these study(s), the following independent audits were performed by or on behalf of GlaxoSmithKline.

Study Number	Type	Conducted by	Centre number	Country	Audit Date
107625	Investigator site	CQA	[redacted]	Japan	31 March - 3 April 2008

Clinical Quality Assurance 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, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

Name: [redacted] **Date:** 11 September 2009

Role: Manager

Clinical Quality Assurance
GlaxoSmithKline Research and Development

Documentation of statistical methods

Refer to the Study 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

This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.

Individual Listings

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****.*

CRFs for SAEs

As the study is still ongoing, the blinding will be maintained for the whole study period. CRFs for SAEs will be provided after unblinding at the time of the annex report.

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

Study Reporting and Analysis Plan Approval

Title:	Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.
eTrack study number	107625
eTrack abbreviated title	Rota 056
Scope:	All data pertaining to the above study
Date:	04Jun2009
Co-ordinating author:	[redacted]
Other author(s):	[redacted]

Approved by:

Director, Worldwide Clinical Development, Rotavirus vaccines	[redacted]	Signature	dd-mmm-yyyy
Clinical Development Manager	[redacted]	Signature	dd-mmm-yyyy
Project Statistician	[redacted]	Signature	dd-mmm-yyyy
Director, Statistical Manager	[redacted]	Signature	dd-mmm-yyyy
Manager, Biometrics, CDOC-B	[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
ELISA	Enzyme Linked Immunosorbent Assay
eTrack	GSK tracking tool
GE	Gastroenteritis
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
HRV	Human Rotavirus
IgA	Immunoglobulin A
IS	Intussusception
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
RV	Rotavirus
SAE	Serious Adverse Event
SAS	Statistical Analysis System

1. LIST OF AMENDMENTS TO THE RAP

No amendment was done

2. INTRODUCTION

This document summarizes the planned statistical analyses (Sections 3 & 4) based on the study features as per Protocol Amendment 1 dated 07-MAY-2007. The changes in the analyses as compared to the Protocol Amendment 1 are provided in section 4. The list of tables/listings to be produced in the statistical report is available in section 5.

3. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

3.1. Primary Endpoints

Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

3.2. Secondary Endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Gastroenteritis (GE) episode for efficacy analysis is defined as diarrhea with or without vomiting leading to a medical intervention.

Severe GE for efficacy analysis: A gastroenteritis episode leading to a medical intervention with a score of 11 or greater on the Vesikari scale.

RV GE for primary efficacy analysis: An episode of any severity GE leading to a medical intervention occurring at least two weeks after dose 2 in which rotavirus other

than vaccine strain is identified in a stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode.

Safety and reactogenicity

- 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/Placebo.
- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Immunogenicity (in the immunogenicity subset N = 60)

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 3.

3.3. Study cohorts to be evaluated

3.3.1. 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 from the immunogenicity subset for whom immunogenicity data are available.
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects.

3.3.2. ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects:

- who received two 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,
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks after Dose 2 of HRV vaccine or placebo,
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

This cohort will be defined for the final report.

3.3.3. ATP cohort for efficacy for second year follow up

The ATP cohort for efficacy will include all subjects from the ATP cohort for efficacy:

- who have follow-up beyond visit 4
- who have not received a vaccine forbidden by or not specified in the protocol

This additional cohort will be defined for the annex report to analyse year 2 efficacy.

3.3.4. ATP cohort for safety

The ATP cohort for safety will include all vaccinated subjects

- who have received at least one dose of study vaccine or placebo,
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

3.3.5. ATP cohort for immunogenicity

The ATP immunogenicity cohort will include all the subjects from the ATP safety cohort in the immuno subset (N=60):

- 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 time point.
- 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 10.5 of the protocol for definition of seronegative subjects.

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 vaccinated 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 vaccinated subjects are excluded from the ATP immunogenicity cohort. In such a case, the total vaccinated cohort analyses will evaluate whether exclusion from the ATP cohort could have biased the results.

The list of applicable elimination codes for each cohort can be found in section 7.

Cohort	**Elimination codes**	**Eli Type**
ATP cohort for safety	1030,1040,1050,1060,1070	MA
ATP cohort for immunogenicity	1030,1040,1050,1060,1070, 2010, 2020, 2040, 2050, 2060, 2070, 2080, 2090,2100, 2120, 2500, 2005	MA
ATP cohort for efficacy	1030, 1040, 1050, 1060,1070, 3010, 3020, 3030	MA
ATP cohort efficacy for second year follow up	1030, 1040, 1050, 1060,1070, 3010, 3020, 3030, 4020	FU

3.4. Derived and transformed data

Demography

For a given subject and a given demographic variable, missing measurement will not be replaced

Efficacy

GE episodes were defined on diarrhoea/gastroenteritis. Two occurrences of GE were classified as separate episodes if there were 5 or more diarrhoea-free days between the episodes. An episode of any severity GE leading to a medical Intervention in which rotavirus other than vaccine strain is identified in a stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode will be classified positive for RV. GE episode without stool sample/result available and with only vaccine strain identified in the associated stool sample will not be considered in the analysis as a RV GE episode leading to a medical Intervention.Analysis of efficacy up to database lock will be censored at last contact in case a subject discontinued the study, at visit 5 or at 31 march 2009, which ever occurred first.

Safety

Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be re-assessed to ensure more accurate reporting of study data by further analysis.

Immunogenicity

The cut-off value of anti-rotavirus IgA antibody is defined by the laboratory before the analysis and is described in Section 5.6.2 of the protocol.

- A seronegative subject is a subject whose antibody concentration is below the cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value.
- Seroconversion is defined as the appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.

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.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

3.5. Data presentation description

The following decimal description will be used for the demography, efficacy, reactogenicity and immunogenicity analyses.

Display Table	**Parameters**	Number of decimal digits
All summaries	% of count, including LL & UL of CI	1
All summaries	% of difference, including LL & UL of CI	2
All summaries	p-value	3
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	2
Immunogenicity	GMC	1
Efficacy	% VE including LL & UL	1

3.6. Group description

The following groups will be used for the statistical analyses.

Study	**Group order in tables**	**Group label in tables**
107625	1	HRV
	2	Placebo

3.7. Final analyses

Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period. This final analysis will be run by an independent analysis center in order to preserve blinding as much as possible. However, due to regulatory requirement associated to a clinical report, fatalities and drop-out will be unblinded. In addition planned summaries may lead to inadvertent unblinding.

An annex report will present the efficacy/safety data up to two years of age.

3.7.1. Analysis of demographics

The mean, median and standard deviation of height in centimetre (cm), weight in kilogram (kg) at visit 1 will be calculated per group and overall.

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo will be calculated per group and overall. The median, mean, range and standard deviation of age in months at Visits 4 and 5 or at last contact if the study visit was not performed will also be calculated per group and overall. The racial and gender composition per group will also be presented.

The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group.

Summary of feeding practice on the day of each study vaccination will be tabulated by group.

3.7.2. Analysis of efficacy

Vaccine efficacy will be calculated, with their 95% CI (see section 3.7.5 for detail methodology) against:

- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to G1 serotype caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to non-G1 serotypes during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

The primary objective will be reached if the lower limit of the 95% confidence interval on vaccine efficacy (conditional method) for the HRV group against any RVGE requiring medical intervention caused wild-type RV strains during the efficacy follow-up period is > 0%.

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE of any aetiology leading to a medical intervention, efficacy against hospitalisation due to GE of any aetiology, efficacy during the period starting from two weeks after Dose 2 until Visit 4). An exploratory analysis will be performed for VE against any and severe RVGE leading to a medical intervention and caused by the circulating wild-type RV strains by cox method.

Vaccine efficacy, derived from a Cox regression model on the time to first event with censoring at the database lock or subjects without event. The model includes the group as

fixed effect [Kalbfleisch, J. D. and Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data* :Wiley].

Incidence rate in a group (P) is computed as the number of subjects reporting at least one event (n)/total follow-up time to a first event censored at the database lock date/visit 5 (T). The associated 95% CI's was obtained considering that n follows a Poisson distribution with P*T parameter.

The number of events prevented by 100 vaccinated infant-years will be obtained from 100 times the difference in the incidence rate. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008]

3.7.3. Analysis of safety

The overall incidence, with exact 95% CI, of any adverse events (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each 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.

The verbatim reports of unsolicited adverse events will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited adverse events occurring within 31-day follow-up period after any doses with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited adverse events rated as grade 3 and for unsolicited adverse events with causal relationship to vaccination.

Serious adverse events reported during the study period will be described in detail.

3.7.4. Analysis of immunogenicity

In a subset of subjects (N = 60)

For each treatment group, at each time point that anti-rotavirus IgA is measured,

- Seroconversion/seropositivity and their exact 95% CI will be calculated.
- GMCs 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 (RCCs).

The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between HRV vaccine and Placebo groups will be computed.

3.7.5. Methodology for computing CI

All CI will be 2 sided 95% CI.

- The exact 95% CIs for a proportion within a group will be calculated from Proc StatXact [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934;26:404-413].
- Proc StatXact will be used to derive the standardized asymptotic 95% CI for the group difference in proportions [ROBERT G. NEWCOMBE , INTERVAL ESTIMATION FOR THE DIFFERENCE BETWEEN INDEPENDENT PROPORTIONS: COMPARISON OF ELEVEN METHODS, Statist. Med. 17, 873-890 (1998), Method 6].
- The 95% CI for geometric mean concentrations (GMCs) will be obtained within each group separately. The 95% CI for the mean of log-transformed concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed concentration.
- The Vaccine Efficacy (VE) will be estimated as 1 – the relative risk. The same transformation will be used to derive the exact CI boundaries from those obtained for the relative risk. The CI for the the relative risk will be based on the method Ca describe in the paper by Man-Lai Tang, Hon Keung Tony Ng Comment on: confidence limits for the ratio of two rates based on likelihood scores: non iterative method, Statistics in Medicine 2004; 23:685-693. This method is also implemented in Proc StatXact 7.0 through the Poisson procedure

3.8. Interim analysis

No interim analysis was planned.

4. CHANGE FROM PROTOCOL

The following are the changes from the protocol.

- The final analysis (Case triggered analysis) will be run by an independent analysis center in order to preserve blinding as much as possible. However, due to regulatory requirement associated to a clinical report, fatalities and dropouts will be unblinded.
- An exploratory analysis will be performed for VE against severe RVGE by cox method.
- A Summary table on co-administered, concomitant vaccinations and concomitant medications received during the study period will be generated.

5. INDIVIDUAL LISTINGS AND TEMPLATE OF TABLES FOR THE FINAL ANALYSIS

5.1. Individual listings

With the exception of fatalities, the following individual listings will be provided without treatment information.

Appendix Table I.A - Elimination codes

Appendix Table I.B - Demography

Appendix Table I.Ci - Dates of birth, Informed consent, Vaccination and blood sampling, Contact

Appendix Table I.Cii - Reason for visit not done

Appendix Table I.D - General medical history - Physical examination

Appendix Table I.E – Study conclusion

Appendix Table I.G - Vaccination procedure

Appendix Table I.J - Reason for non-Eligibility

Appendix Table I.K - Feedings Practice

Appendix Table II.B - Solicited general symptoms

Appendix Table II.Ci - Unsolicited adverse events within 31-day (Days 0-30) days post-vaccination

Appendix Table II.Cii - Unsolicited adverse events after 31-day (Days 0-30) days post-vaccination

Appendix Table II.Ciii – Fatalities up to database lock

Appendix Table II.Di - Concomitant medications

Appendix Table II.Dii - Concomitant vaccinations

Appendix Table III.A – Immunogenicity results

Appendix Table IV.B – Gastroenteritis stool collection results

Appendix Table V.A - Detailed information of gastroenteritis episodes

5.2. List of tables for the final analysis

If 28 RVGE cases leading to medical intervention are reported before all the subjects reaching two years of age, the following tables will be generated till that database lock point.

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 ATP analyses (reactogenecity and immunogenicity) with reasons for exclusion.	CR	%ELIMLIST
Table D 2	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	CR	%ELIMLIST
Table D 3	Number of subjects by center (Total vaccinated cohort)	ST	%CENTER
Table D 4	Number of subjects at each visit and list of withdrawn subjects upto database lock (Total vaccinated cohort)	ST	%DROPOUT
Table D 5	Number of subjects entered, completed and withdrawn with reason for withdrawal at database lock (Total vaccinated cohort)	CR	%DROP_SUM
Table D 6	Deviation from specifications for age and intervals between study visits (Total vaccinated cohort)	ST	%INT_VAL
Table D 7	Deviation from specifications for age and intervals between study visits (ATP cohort for immunogenicity)	ST	%INT_VAL
Table D 8	Minimum and maximum activity dates (Total vaccinated cohort)	WT	%DATE

Table D 9	Summary of demographic characteristics (Total vaccinated cohort)	ST	%DEMOGRA
Table D 10	Summary of demographic characteristics (ATP cohort for Immunogenicity)	CR	%DEMOGRA
Table D 11	Summary of demographic characteristics (ATP cohort for Efficacy)	CR	%DEMOGRA
Table D 12	Summary of feeding practices at Dose 1 and at Dose 2 of HRV vaccine or Placebo (Total Vaccinated Cohort)	CR	%FREQ_DIS
Table D 13	Summary of feeding practices at Dose 1 and at Dose 2 of HRV vaccine or Placebo (ATP Cohort for Efficacy)	ST	%FREQ_DIS
Table D 14	Summary of co-administered vaccination by dose (Total vaccinated cohort)	ST	%FREQ_DIS
Table D 15	Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)	ST	%FREQ_DIS
Table D 16	Compliance (Total Vaccinated Cohort)	ST	%COMPLI
Table D 17	Subjects unblinded before database lock (date) (Total Vaccinated cohort)	WT	%UNBLIND
Table CTRS 1	Demography for CTRS	CTRS	%CTR_DEMOG

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure

5.2.2. For Efficacy Analysis:

The tables and graphs below will be done for the period from 2 weeks after dose 2 until database lock, for the ATP cohort for efficacy.

TABLE # in reference of section 5.3	Table Title	Final analysis
Table E 1	Percentage of subjects with vaccine virus in gastroenteritis stool samples collected in case of GE episode from Dose 1 up to database lock (Total vaccinated cohort)	ST
Table E 2	Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy	CR*
Table E 3	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to database lock by severity using the 20-point Vesikari scale - ATP cohort for efficacy	CR*
Table E 4	Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy	ST*
Table E 5	Percentage of subjects with severe RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy	ST*
Table E 6	Number of RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy	ST
Table E 7	Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy	ST
Table E 8	Characteristics (based on Vesikari scale) of severe RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by main RV types and overall - ATP cohort for efficacy	ST
Table E 9	Duration (in years) of efficacy follow-up period from 2 weeks after Dose 2 up to database lock – ATP cohort for efficacy	ST*
Table E 10	Percentage of subjects reporting any RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy	CR*
	Percentage of subjects reporting any RV GE episode and efficacy	CR*

Table E 11	of the vaccine from 2 weeks after Dose 2 up to database lock, by RV types - ATP cohort for efficacy	
Table E 12	Percentage of subjects reporting severe RV GE (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy	CR*
Table E 13	Percentage of subjects reporting severe RV GE episode (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock, by RV types - ATP cohort for efficacy	CR*
Table E 14	Percentage of subjects hospitalised due to RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock- ATP cohort for efficacy	CR
Table E 15	Efficacy of the vaccine against any RV GE from 2 weeks after Dose 2 up to database lock, by Cox - ATP cohort for efficacy	ST*
Table E 16	Efficacy of the vaccine against severe RV GE from 2 weeks after Dose 2 up to database lock, by Cox - ATP cohort for efficacy	ST
Table E 17	Percentage of subjects reporting any and severe RVGE episodes and risk difference of the vaccines from 2 weeks after dose 2 upto database lock - ATP cohort for efficacy	ST*
Table E 18	Percentage of subjects reporting all cause GE and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy	ST
Figure E 1	Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to database lock – ATP cohort for efficacy	ST*
Figure E 2	The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to database lock- ATP cohort for efficacy	ST*
Figure E 3	The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to database lock- ATP cohort for efficacy	ST

CR = within the clinical report
ST = as a supplementary table or figure
WT = as a working or CTRS table or figure
*=The tables and graphs listed above will also be done for the period from Dose 1 up to database lock, for the Total vaccinated cohort. The resulting tables will appear as supplemental tables.

5.2.3. For Reactogenicity and Safety Analysis:

TABLE # in reference of section 5.3	Table Title	Final analysis	Macro
Table R 1	Number and percentage of subjects who received vaccine dose(s) (Total vaccinated cohort)	CR *	%EXPO
Table R 2	Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 8-day (Days 0-7) solicited follow-up period(Total vaccinated cohort)	CR*	%LOCGEN
Table R 3	Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)	ST*	%LOCGEN
Table R 4	Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)	ST*	%LOCGEN
Table R 5	Percentage of subjects reporting each solicited general symptom included those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period, for each dose (Total vaccinated cohort)	CR*	%FREQ
Table R 6	Percentage of doses and subjects reporting each solicited general symptom included those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)	ST*	%FREQ
Table R 7	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total	CR*	%UNSOL

	vaccinated cohort)		
Table R 8	Percentage of doses with unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)	ST*	%UNSOL
Table R 9	Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)	CR*	%UNSOL
Table R 10	Percentage of doses with grade 3 unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)	ST*	%UNSOL
Table R 11	Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class that are causally related to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)	CR*	%UNSOL
Table R 12	Percentage of doses with unsolicited symptoms classified by MEDDRA Primary System Organ Class that are causally related to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)	ST*	%UNSOL
Table R 13	Percentage of subjects with SAE's classified by MedDRA system organ class during the study period (Total vaccinated cohort)	CR*	%UNSOL
Table R 14	Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after vaccination by type (Total vaccinated cohort)	ST*	%CMED_INC
Table R 15	Number and percentage of doses and of subjects who took at least one concomitant medication during the study	ST*	%CMED_INC

	period by type (Total vaccinated cohort)		
Table R 16	Listing of SAEs (Total vaccinated cohort)	ST*	%SAE
Table R 17	Listings of fatalities from dose 1 of HRV or Placebo up to database lock (Total vaccinated cohort)	ST*	%FATAL_LS
Table CTRS 1	Number (%) of subjects with serious adverse events (Total vaccinated cohort)	CTRS	%CTR_SAE

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working table or figure
*: a complementary analysis based on the ATP cohort for safety will be provided if more than 5% of the vaccinated subjects are excluded from that cohort. The resulting tables will appear as supplemental tables.

5.2.4. For Immunogenicity Analysis:

TABLE # in reference of section 5.3	Table Title	Final Analysis	Macro
Table I 1	Anti-rotavirus IgA antibody GMC and seroconversion rates from a subset of subjects (ATP cohort for immunogenicity)	CR*	%GMT
Table I 2	Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies at visit 3 from a subset of subjects (ATP cohort for immunogenicity)	ST*	%GMT
Figure I 1	Reverse cumulative curves for anti-rotavius IgA antibody concentrations at visit 3 from a subset of subjects (ATP cohort for immunogenicity)	ST*	%REVCUM
Table I 3	Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum anti-rotavirus IgA antibody from a subset of subjects (ATP cohort of immunogenicity).	CR*	%SP_CI

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure
*: a complementary analysis based on the Total Vaccinated cohort for immuno subset (N=60) will be provided if more than 5% of the vaccinated subjects with immunogenicity results available are excluded from that cohort. The resulting tables will appear as supplemental tables.

5.3. Template of tables for the Final analysis

The following tables/figures provide lay-out tables for the statistical analyses.

Table D 1 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses (reactogenecity and immunogenicity) with reasons for exclusion.

Title	Total				HRV				Placebo			
	N	n	s	%	N	n	s	%	N	n	s	%
Total enrolled cohort												
Study vaccine dose not administrated but subject number allocated (code 1030)												
Total vaccinated cohort												
Administration of vaccine(s) forbidden in the protocol (code 1040)												
Randomisation code broken at the investigator site (code 1060)												
Study vaccine dose not administered according to protocol (code 1070)												
ATP safety cohort												
Subjects not planned in the protocol to be bled for their all blood sampling visits(2005)												
Initially seropositive OR initially unknown antibody status(code 2020)												
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)												
Essential serological data missing (code 2100)												
Obvious incoherence or abnormality or error in data (code 2120)												
ATP immunogenicity cohort												

% = 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
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
Codes are listed based on a ranking order

Table D 2 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

	Total			HRV		Placebo	
Title	n	s	%	n	s	n	s
Total enrolled cohort							
Study vaccine dose not administrated but subject number allocated (code 1030)							
Total vaccinated cohort							
Randomisation code broken at the investigator site (code 1060)							
Study vaccine dose not administered according to protocol (code 1070)							
At least one study vaccine dose not administered (code 3010)							
Subjects not entered in to the surveillance period of the first efficacy follow-up period(code 3020)							
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response (code 3030)							
ATP efficacy cohort - first period/ combined period							
Subjects not entered in to the surveillance period of the second efficacy follow-up period (Code 4020) ATP efficacy cohort - second period							

Note: Subjects may 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 vaccinated cohort
The ATP efficacy cohort for the first efficacy follow-up period and for combined efficacy follow-up periods include all vaccinated subjects with no elimination codes beginning with one thousand or three thousand. The ATP efficacy cohort for the second efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one thousand, three thousand or four thousand.

Table D 3 Number of subjects by center (Total vaccinated cohort)

Center	HRV	Placebo	Total	
	n	n	n	%

- 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.

Table D 4 Number of subjects at each visit and list of withdrawn subjects upto database lock (Total vaccinated cohort)

Group	Visit	N	Withdrawn Subject	Reasons for withdraw
HRV	Visit1			
	Visit2			
	Visit3			
	Visit 4			
Placebo	Visit1			
	Visit2			
	Visit3			
	Visit 4			

N = number of subjects in each vaccine group

Table D 5 Number of subjects entered, completed and withdrawn with reason for withdrawal at database lock (Total vaccinated cohort)

	Group		
	HRV	Placebo	Total
Number of subjects vaccinated			
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			

vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed the last study visit
withdrawn = number of subjects who did not come for the last study visit

Table D 6 Deviation from specifications for age and intervals between study visits (Total vaccinated cohort)

Group		Age	VAC_1-VAC_2		VAC_2-BL	
		Protocol	Protocol	Adapted	Protocol	Adapted
		from 6 to 14 W	from 30 to 48 D	from *21* D To *48* D	from 30 to 48 D	from *21* D To *48* D
HRV	N n % range	/		/		/
Placebo	N n % range	/	/	/		/

VIS = Visit
W = Weeks D = Days
n = number of subjects out of the specified interval.
% = proportion of subjects out of the specified interval among with subjects present at the considered visits.
% (for age) = proportion of subjects out of the specified interval using as denominator the number of subjects enrolled.

Table D 7 Deviation from specifications for age and intervals between study visits (ATP cohort for immunogenicity)

See the template Table D 7

Table D 8 Minimum and maximum activity dates (Total vaccinated cohort)

Visit number	Activity number	Minimum date	Maximum date
1 2 3 4 5			

Table D 9 Summary of demographic characteristics (Total vaccinated cohort)

Characteristics	Parameters or Categories	HRV N= XXX		Placebo N= XXX		Total N= XXX	
		Value or n	%	Value or n	%	Value or n	%
Age(w) at dose 1 of HRV/placebo	Mean SD Median Minimum Maximum						
Age (w) at dose 2 of HRV/Placebo	Mean						
	SD						
	Median Maximum						
	Minimum						
Age (months) at database lock point/last contact	Mean						
	SD						
	Median						
	Maximum						
	Minimum						
Gender	Female Male						
Race	Black White/caucasian Oriental Arabic/north East/south east asian South asian American hispanic Japanese Other						
Height at visit 1(cm)	Mean SD						
	Median						
Weight at visit 1 (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(W)= age expressed in Weeks

Table D 10 Summary of demographic characteristics (ATP cohort for Immunogenicity)

See template Table D 9

Table D 11 Summary of demographic characteristics (ATP cohort for Efficacy)

See template Table D 9

Table D 12 Summary of feeding practices at Dose 1 and at Dose 2 of HRV vaccine or Placebo (Total Vaccinated Cohort)

	Feeding Practice	HRV			Placebo		
		N	n	%	N	n	%
Dose 1	Breast-fed						
	Formula-fed						
	Solid-food						
	Breast-fed and Formula-fed						
	Breast-fed and Solid food						
	Formula-fed and Solid food						
	Breast-fed, Formula-fed and Solid food						
Dose 2	Breast-fed						
	Formula-fed						
	Solid-food						
	Breast-fed and Formula-fed						
	Breast-fed and Solid food						
	Formula-fed and Solid food						
	Breast-fed, Formula-fed and Solid food						
Combined doses	Breast-fed						
	Formula-fed						
	Solid-food						
	Breast-fed and Formula-fed						
	Breast-fed and Solid food						
	Formula-fed and Solid food						
	Breast-fed, Formula-fed and Solid food						
	Other						

For each dose: N=number of subjects who received the considered dose.
For combined dose: N=number of subject having received the two doses.
n(%)=number(percentage) of subjects with the specified feeding criteria.
Combined = Feeding practices at both the doses.

Other= the subjects who have not had the above listed feeding types “at both the doses”.

Table D 13 Summary of feeding practices at Dose 1 and at Dose 2 of HRV vaccine or Placebo (ATP Cohort for Efficacy)

See template Table D 12

Table D 14 Summary of co-administered vaccination by dose (Total vaccinated cohort)

	HRV N = xxx		Placebo N = xxx		Total N = xxx	
Characteristics	Value or n	%	Value or n	%	Value or n	%
Dose 1						
Any						
BCG						
DTP						
HBV						
HIB						
OPV						
Dose 2						
Any						
BCG						
DTP						
HBV						
HIB						
OPV						

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

Table D 15 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)

Before Dose 1									
	HRV (N=xxx)			Placebo (N=xxx)			Total N=xxx		
Characteristics	#	n	%	#	n	%	#	N	%
Any									
BCG									
DTP									
HBV									
HIB									
OPV									
Between dose 1 and dose 2§									
	HRV (N=xxx)			Placebo (N=xxx)			Total N=xxx		
Characteristics	#	n	%	#	n	%	#	N	%
Any									
BCG									
DTP									
HBV									
HIB									
OPV									
Between dose 2 and visit 3*									
	HRV (N =xxx)			Placebo (N=xxx)			Total N=xxx		
Characteristics	#	n	%	#	n	%	#	N	%
Any									
BCG									
DTP									
HBV									
HIB									
OPV									

N = Between Dose 1 and Dose 2 : total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and visit 3: total number of subjects having received dose 2 of HRV/placebo

#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV/placebo doses

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 if dose 2 of HRV/placebo was not administered

*= up to last contact if visit 3 was not done

Table D 16 Compliance (Total Vaccinated Cohort)

Number of Doses	Group	Doses NOT according to protocol	Number of general SS	Compliance % General
1	HRV			
	Placebo			
2	HRV			
	Placebo			

SS = Symptom sheets used for the collection of general solicited AEs
Compliance % = (number of subjects returning a symptom sheet (SS)/number of doses) x 100

Table D 17 Subjects unblinded before database lock (date) (Total Vaccinated cohort)

Group	Subject Number	Date of unblinding	Previous dose	Day of onset	Reason

Day of onset: relative to previous dose administered (administration day is day 0)

Table E 1 Percentage of subjects with vaccine virus in gastroenteritis stool samples collected in case of GE episode from Dose 1 up to database lock (Total vaccinated cohort)

Group				95%CI	
	N	n	%	LL	UL
HRV					
Placebo					

N = number of subjects having received at least one dose
n/% = number/percentage of subjects with vaccine virus in gastroenteritis stool samples collected during the study
95% CI, L.L and U.L = lower and upper limits of the exact 95% CI

Table E 2 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

Event	Total number of episodes reported	HRV N =xxx		Placebo N =xxx	
		n	%	n	%
GE	1 2 … Any				
RV GE	1 2 … Any				
Severe GE	1 2 … Any				
Severe 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
Any = number and percentage of subjects reporting at least one specified symptom = sum of the "Total number of episode reported" = 1 to …

Table E 3 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to database lock by severity using the 20-point Vesikari scale - ATP cohort for efficacy

		HRV		Placebo	
Event	Severity using the 20-point Vesikari scale	n	%	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

Table E 4 Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy

Serotype	HRV n	%	Placebo n	%
	N=		N=	
Any G1/P8 G2/P4				

N = number of subjects included in each group, for the considered efficacy follow-up period
n/% = number/percentage of subjects reporting at least once the specified serotype in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episode, whatever the serotype

Table E 5 Percentage of subjects with severe RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy

See template for Table E 4

Table E 6 Number of RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - 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

Table E 7 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by G and P type - ATP cohort for efficacy

Serotype	HRV		Placebo	
	n	%	n	%
	N'=		N'=	
G1 wild type				
G2				
G4 and G9				
....				

N'= number of severe RV GE episodes reported in the considered efficacy period
n/%= number/percentage of severe RV GE episodes reported in the considered efficacy period, by serotype

Table E 8 Characteristics (based on Vesikari scale) of severe RV GE episodes reported from 2 weeks after Dose 2 up to database lock, by main RV types and overall - ATP cohort for efficacy

			HRV N'= 24		Placebo N'= 94	
Serotype (Main serotype and overall)	Characteristics	Parameters or categories	Value or n	%	Value or n	%
	Vesikari severity score	Mean		-		-
		SD		-		-
		Median		-		-
		Minimum		-		-
		Maximum		-		-
	Duration of looser than normal stools (days)	0 day				
		1-4 days				
		5				
		≥ 6 days				
	Maximum number of . than normal stools/day	0				
		1-3				
		4-5				
		≥ 6				
	Duration of vomiting (days)	0 day				
		1 day				
		2 days				
		≥ 3 days				
	Maximum number of episodes of vomiting/24day	0				
		1				
		2-4				
		≥ 5				
	Maximum fever reported /day (measured rectally)	< 37.1°C				
		37.1-38.4°C				
		38.5-38.9°C				
		≥ 39°C				
	Treatment	none				
		Rehydration				
		Hospitalisation				
	Dehydration	none				
		1-5%				
		≥ 6%				

N'= number of severe 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 E 9 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 2 up to database lock – 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

Table E 10 Percentage of subjects reporting any RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV									
Placebo									

N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode
%= percentage of subjects reporting at least one RV GE episode
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases

Table E 11 Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock, by RV types - ATP cohort for efficacy

		n/N					Vaccine Efficacy			P-Value
					95%CI			95%CI		
Serotype	Group	N	n	%	LL	UL	%	LL	UL	
G1 wild type	HRV Placebo									
G2	HRV Placebo									
…….	HRV Placebo									
Pooled Non G1 (G2, …….)	HRV Placebo									

N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode
%= percentage of subjects reporting at least one RV GE episode
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases

Table E 12 Percentage of subjects reporting severe RV GE (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

See template for Table E 10

Table E 13 Percentage of subjects reporting severe RV GE episode (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock, by RV types - ATP cohort for efficacy

See template for

Table E 11

Table E 14 Percentage of subjects hospitalised due to RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock- ATP cohort for efficacy

See template for Table E 10

Table E 15 Efficacy of the vaccine against any RV GE from 2 weeks after Dose 2 up to database lock, by Cox - ATP cohort for efficacy

				n/T			Vaccine Efficacy			
			T		95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	P-value
Any RV GE of any wild gtype										
HRV										
Placebo										
Any RV GE of G1 wild type										
HRV										
Placebo										
Any RV GE of pooled Non G1 (G2, G3, G4, ...)										
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
T= sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the considered efficacy period
n/T= person-year rate of severe RV GE in each group
LL, UL = 95 % Lower and Upper confidence limits

Table E 16 Efficacy of the vaccine against severe RV GE from 2 weeks after Dose 2 up to database lock, by Cox - ATP cohort for efficacy

See template for

Table E 15

Table E 17 Percentage of subjects reporting any and severe RVGE episodes and risk difference of the vaccines from 2 weeks after dose 2 upto database lock - ATP cohort for efficacy

				Person-year rate			Risk difference (Placebo - HRV)		
Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
Any RVGE									
HRV									
Placebo									
Severe RVGE									
HRV									
Placebo									

N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
RD=risk difference (Placebo-HRV) .

Table E 18 Percentage of subjects reporting all cause GE and efficacy of the vaccine from 2 weeks after Dose 2 up to database lock - ATP cohort for efficacy

See template for Table E 10

Figure E 1 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to database lock – ATP cohort for efficacy

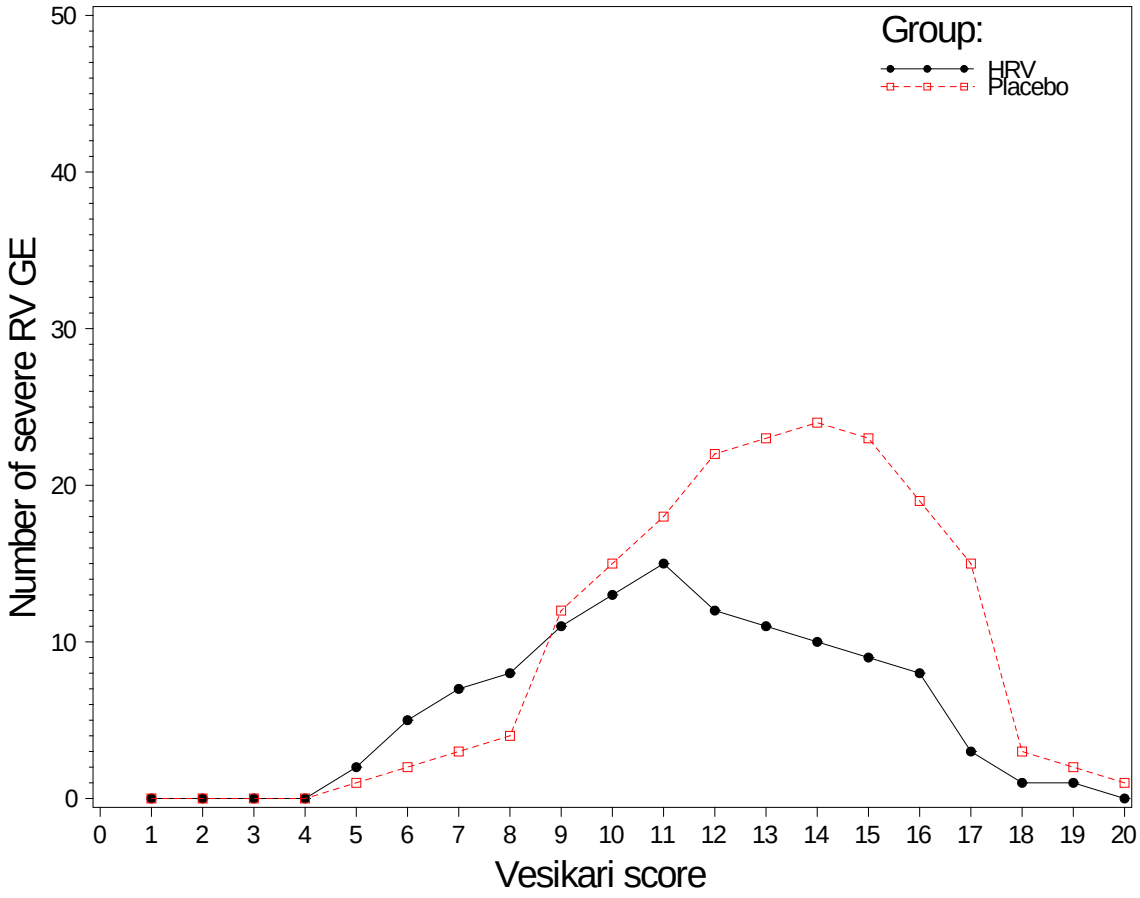


Figure E 2 The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to database lock- ATP cohort for efficacy

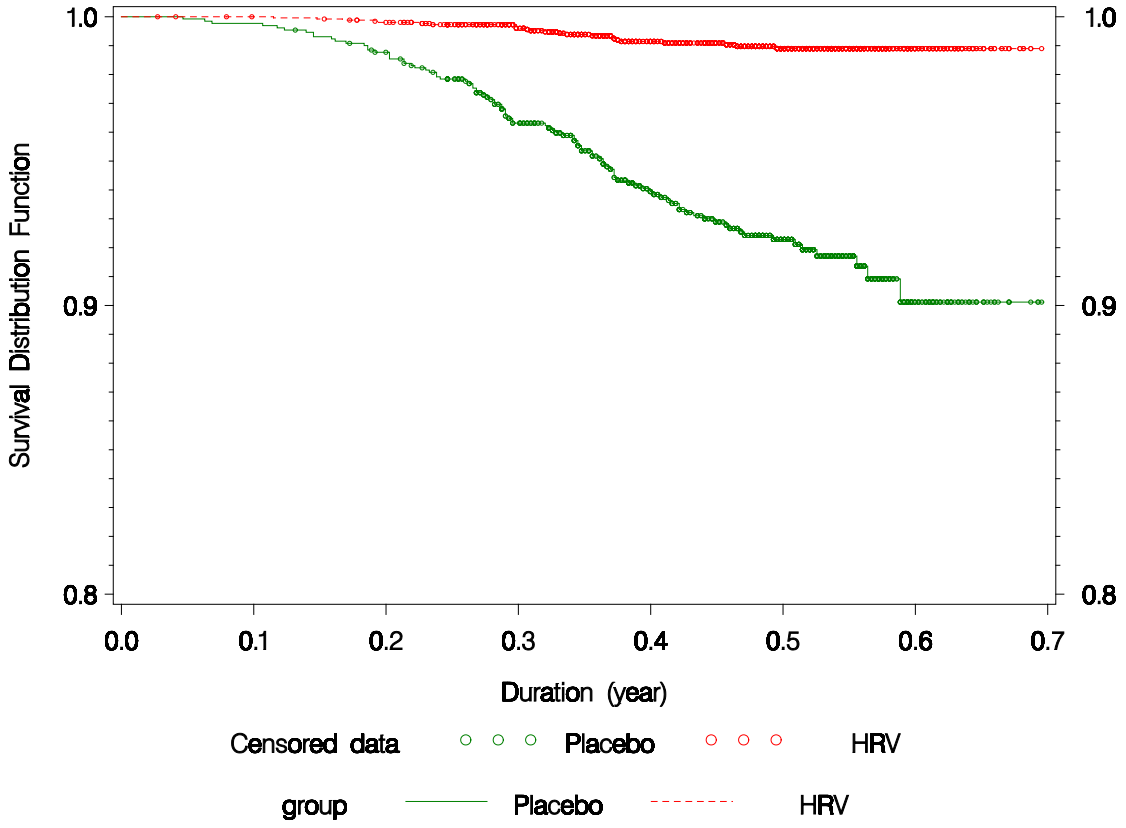


Figure E 3 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to database lock- ATP cohort for efficacy

See template for Figure E 2

Table R 1 Number and percentage of subjects who received vaccine dose(s) (Total vaccinated cohort)

Total number Of doses received	HRV (N = XXX)		Placebo (N = XXX)		Total (N = XXX)	
	n	%	n	%	n	%
1						
2						
Any						

N = number of subjects in each group or in total included in the considered cohort
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

Table R 2 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 8-day (Days 0-7) solicited follow-up period(Total vaccinated cohort)

		Any symptom				
					95% CI	
	Group	N	n	%	LL	UL
Dose 1	HRV					
	Placebo					
Dose 2	HRV					
	Placebo					
Overall/dose	HRV					
	Placebo					
Overall/subject	HRV					
	Placebo					

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table R 3 Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)

See template for Table R 2

Table R 4 Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period (Total vaccinated cohort)

See template for Table R 2

Table R 5 Percentage of subjects reporting each solicited general symptom included those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period, for each dose (Total vaccinated cohort)

		HRV					Placebo				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1											
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										
Cough/runny nose	Total										
	Grade 3										
	Related										
Dose 2											
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										
Cough/runny nose	Total										
	Grade 3										
	Related										

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting at least once the symptom
For Overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table R 6 Percentage of doses and subjects reporting each solicited general symptom included those graded 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0-7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

		HRV					Placebo				
					95% CI					95% CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Overall/dose											
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										
Cough/runny nose	Total										
	Grade 3										
	Related										
Overall/subject											
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										
Cough/runny nose	Total										
	Grade 3										
	Related										

For overall/subject:

N= number of subjects with at least one administered dose

n/%= number/percentage of subjects reporting at least one symptom

For overall/dose:

N = number of administered doses

n/% = number/percentage of doses followed by at least one symptom

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

Table R 7 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

Primary System Organ	HRV N=XX			Placebo N=XX			
Class (CODE)	n	%	95% CI	n	%	95% CI	
			LL UL			LL	UL
At least one symptom							
Gastrointestinal disorders (10017947)							
General disorders and administration site conditions (10018065)							
Infections and infestations (10021881)							
Injury, poisoning and procedural complications (10022117)							
Musculoskeletal and connective tissue disorders (10028395)							
Nervous system disorders (10029205)							
Psychiatric disorders (10037175)							
Respiratory, thoracic and mediastinal disorders (10038738)							
Skin and subcutaneous tissue disorders (10040785)							

At least one symptom = At east one symptom experienced regardless of the System Organ Class
N = Number of subjects having received at least one dose
n/% = Number / percentage of subjects reporting at least once a specified symptom within 31 days after vaccination day 0 to day 30
95% CI = Exact 95% confidence interval

Table R 8 Percentage of doses with unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

Primary System Organ	HRV N=XX			Placebo N=XX			
Class (CODE)	n	%	95% CI	n	%	95% CI	
			LL UL			LL	UL
At least one symptom							
Gastrointestinal disorders (10017947)							
General disorders and administration site conditions (10018065)							
Infections and infestations (10021881)							
Injury, poisoning and procedural complications (10022117)							
Musculoskeletal and connective tissue disorders (10028395)							
Nervous system disorders (10029205)							
Psychiatric disorders (10037175)							
Respiratory, thoracic and mediastinal disorders (10038738)							
Skin and subcutaneous tissue disorders (10040785)							

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of administered doses
n/% = number/percentage of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table R 9 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

See template for Table R 7

Table R 10 Percentage of doses with grade 3 unsolicited symptoms classified by MEDDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

See template for Table R 8

Table R 11 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEDDRA Primary System Organ Class that are causally related to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

See template for Table R 7

Table R 12 Percentage of doses with unsolicited symptoms classified by MEDDRA Primary System Organ Class that are causally related to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

See template for Table R 8

Table R 13 Percentage of subjects with SAE's classified by MedDRA system organ class during the study period (Total vaccinated cohort)

See template for Table R 7

Table R 14 Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 7 after vaccination by type (Total vaccinated cohort)

	HRV					Placebo				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1										
Any Any antipyretic Prophylactic antipyretic Any antibiotic										
Dose 2										
Any Any antipyretic Prophylactic antipyretic Any antibiotic										
Overall/dose										
Any Any antipyretic Prophylactic antipyretic Any antibiotic										
Overall/subject										
Any Any antipyretic Prophylactic antipyretic Any antibiotic										

For each dose and overall/subject:

N= number of subjects with at least one administered dose

n/%= number/percentage of subjects who started to take the specified concomitant medication at least once during the mentioned period

For overall/dose:

N= number of administered doses

n/%= number/percentage of doses after which the specified concomitant medication was started at least once during the mentioned period

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

Table R 15 Number and percentage of doses and of subjects who took at least one concomitant medication during the study period by type (Total vaccinated cohort)

See template for Table R 15

Table R 16 Listing of SAEs (Total vaccinated cohort)

Pid	Case Id	Age (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome

Age (Week) = Age (Week) at SAE onset

Table R 17 Listings of fatalities from dose 1 of HRV or Placebo up to database lock (Total vaccinated cohort)

Group	dose	Day since last dose	Pid	Case Id	Sex	Day since dose 1	date of death	Age at death (days)	Treatment	Verbatim

Table I 1 Anti-rotavirus IgA antibody GMC and seroconversion rates from a subset of subjects (ATP cohort for immunogenicity)

Group	Timing	N	≥ 20 U/ML			GMC		
			n	%	95% CI LL UL	Value	95% CI LL	UL
HRV	Pre							
	PII(M2)							
Placebo	Pre							
	PII(M2)							

GMC = geometric mean antibody concentration, calculated for all subjects. Antibody concentrations below the cut-off of the assays were given an arbitrary value of one half the cut-off for the purpose of calculating the GMC.
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(M2) = two months after the first dose (Visit 3)

Table I 2 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies at visit 3 from a subset of subjects (ATP cohort for immunogenicity)

		GMC			
				95% CI	
Group	Timing	N	value	LL	UL
HRV	Pre				
	PII(M2)				
Placebo	Pre PII(M2)				

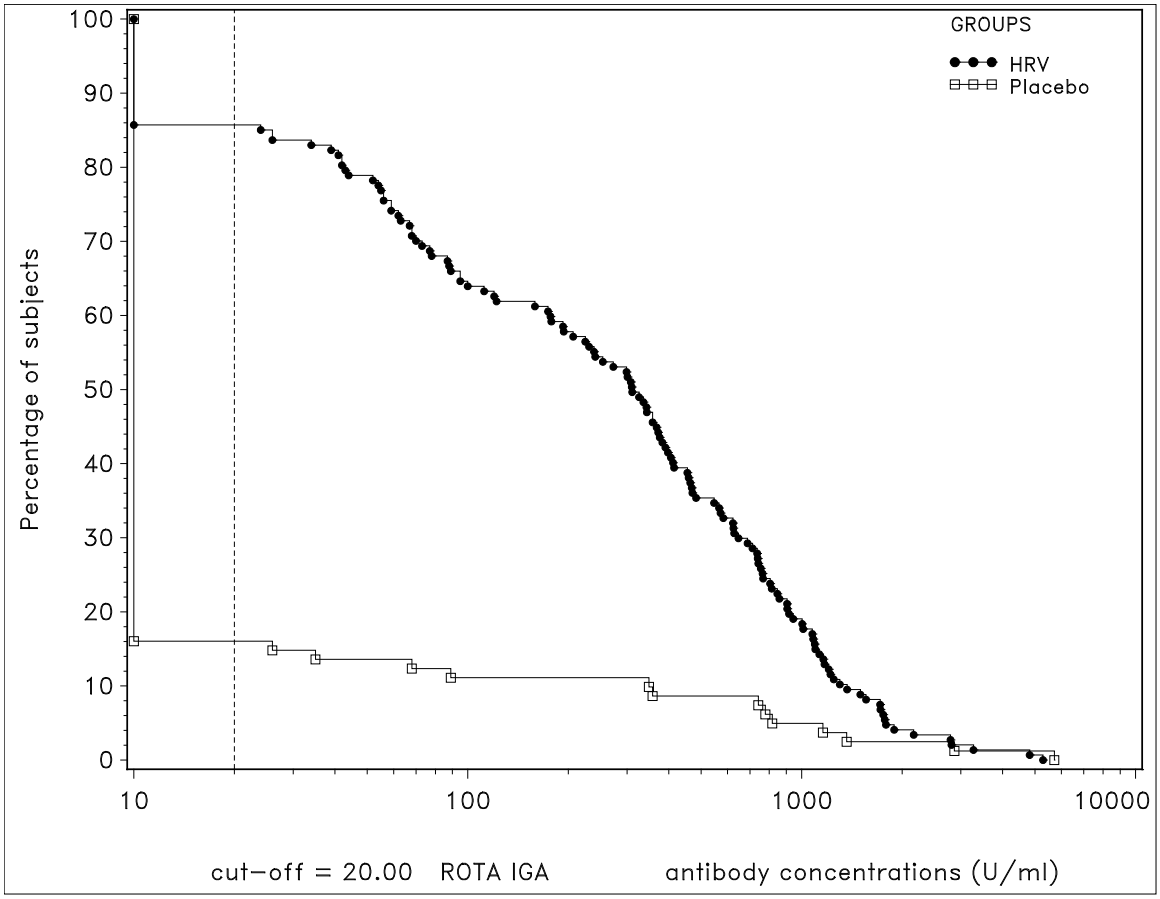
GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who seroconverted for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PII(M2) = two months after the first dose (Visit 3)

Table I 3 Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum anti-rotavirus IgA antibody from a subset of subjects (ATP cohort of immunogenicity).

Group	N	%	Group	N	%	Difference in seroconversion rate			
						Group Difference	Value %	95% CI LL	UL
HRV			Placebo			HRV minus Placebo			

Notes:
N = number of subjects with available results
% = percentage of subjects who seroconverted at visit 3
95%CI = asymptotic standardised 95% confidence interval; LL = lower limit; UL = upper limit

Figure I 1 Reverse cumulative curves for anti-rotavius IgA antibody concentrations at visit 3 from a subset of subjects (ATP cohort for immunogenicity)



6. INDIVIDUAL LISTINGS AND TEMPLATE OF TABLES FOR THE ANNEX (A) ANALYSIS

6.1. Individual listings for the annexe analysis (note that all listings will be generated with the treatment information as the final report will not provide treatment group information)

All individual listings will provide treatment information.

Appendix Table I.A - Elimination codes

Appendix Table I.B - Demography

Appendix Table I.Ci - Dates of birth, Informed consent, Vaccination and blood sampling, Contact

Appendix Table I.Cii - Reason for visit not done

Appendix Table I.D - General medical history - Physical examination

Appendix Table I.E – Study conclusion

Appendix Table I.G - Vaccination procedure

Appendix Table I.J - Reason for non-Eligibility

Appendix Table I.K - Feedings Practice

Appendix Table II.B - Solicited general symptoms

Appendix Table II.Ci - Unsolicited adverse events within 31-day (Days 0-30) days post-vaccination

Appendix Table II.Cii - Unsolicited adverse events after 31-day (Days 0-30) days post-vaccination

Appendix Table II.Ciii – Fatalities

Appendix Table II.Di - Concomitant medications

Appendix Table II.Dii - Concomitant vaccinations

Appendix Table III.A – Immunogenicity results

Appendix Table IV.B – Gastroenteritis stool collection results

Appendix Table V.A - Detailed information of gastroenteritis episodes

6.2. List of tables for the annex (A) analysis

6.2.1. For Demographics Analysis:

TABLE # in reference of section **6.3**	Table Title	Annexe analysis	Macro
Table D(A) 1	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	CR	%ELIMLIST
Table D(A) 2	Number of subjects at each visit and list of withdrawn subjects (Total vaccinated cohort)	ST	%DROPOUT
Table D(A) 3	Number of subjects entered, completed and withdrawn with reason for withdrawal at visit 4 (Total vaccinated cohort)	CR	%DROP_SUM
Table D(A) 4	Number of subjects entered, completed and withdrawn with reason for withdrawal at visit 5 (Total vaccinated cohort)	CR	%DROP_SUM
Table D(A) 5	Minimum and maximum activity dates (Total vaccinated cohort)	WT	%DATE
Table D(A) 6	Summary of demographic characteristics (Total vaccinated cohort)	ST	%DEMOGRA
Table D(A) 7	Summary of demographic characteristics (ATP cohort for Efficacy)	CR	%DEMOGRA
Table D(A) 8	Subjects unblinded before database lock (date) (Total Vaccinated cohort)	ST	%UNBLIND
Table CTRS 1	Demography for CTRS	CTRS	%CTR_DEMOG

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure

6.2.2. For Efficacy Analysis:

The tables and graphs below will also be done for the period from 2 weeks after dose 2 until Visit 5, for the ATP cohort for efficacy.

The tables and graphs below will also be done for the period from Visit 4 up to Visit 5, for the ATP cohort for efficacy for second year follow up.

TABLE # in reference of section **6.3**	Table Title	Annexe analysis
Table E(A) 1	Percentage of subjects with vaccine virus in gastroenteritis stool samples collected in case of GE episode from Dose 1 up to visit 5 (Total vaccinated cohort)	ST
Table E(A) 2	Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 2 up to visit 4 - ATP cohort for efficacy	CR*
Table E(A) 3	Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to visit 4- ATP cohort for efficacy	ST*
Table E(A) 4	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to visit 4 by severity using the 20-point Vesikari scale - ATP cohort for efficacy	CR*
Table E(A) 5	Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy	CR*
Table E(A) 6	Percentage of subjects with severe RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy	CR*
Table E(A) 7	Number of RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy	ST
Table E(A) 8	Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy	ST
Table E(A) 9	Characteristics (based on Vesikari scale) of severe RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by main RV types and overall - ATP cohort for efficacy	ST
Table E(A) 10	Duration (in years) of efficacy follow-up period from 2 weeks after	ST*

	Dose 2 up to visit 4 – ATP cohort for efficacy	
Table E(A) 11	Percentage of subjects reporting any RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4 - ATP cohort for efficacy	CR*
Table E(A) 12	Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4, by RV serotype - ATP cohort for efficacy	CR*
Table E(A) 13	Percentage of subjects reporting severe RV GE (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4 - ATP cohort for efficacy	CR*
Table E(A) 14	Percentage of subjects reporting severe RV GE episode (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4, by RV serotype - ATP cohort for efficacy	CR*
Table E(A) 15	Percentage of subjects hospitalized due to RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP efficacy cohort	ST*
Table E(A) 16	Percentage of subjects reporting all cause GE and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy	ST
Table E(A) 17	Percentage of subjects reporting all cause Severe GE and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy	ST
Table E(A) 18	Percentage of subjects hospitalized due to GE efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy	ST
Table E(A) 19	Percentage of subjects reporting severe RV GE episodes with a score $\geq$X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy	ST
Table E(A) 20	Efficacy of the vaccine against severe RV GE from 2 weeks after Dose 2 up to visit 5, by Cox - ATP cohort for efficacy	ST*
Table E(A) 21	Efficacy of the vaccine against any RV GE from 2 weeks after Dose 2 up to visit 5, by Cox - ATP cohort for efficacy	ST*
Table E(A) 22	Percentage of subjects reporting any and Severe RVGE episodes and risk difference of the vaccines from 2 weeks post dose 2 to visit 4 - ATP cohort for efficacy	ST

Figure E(A) 1	Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to visit 4 – ATP cohort for efficacy	ST
Figure E(A) 2	Efficacy of the vaccine against severe RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 2 up to Visit 4 – ATP cohort for efficacy	ST
Figure E(A) 3	The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to visit 5- ATP cohort for efficacy	ST
Figure E(A) 4	The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to visit 5- ATP cohort for efficacy	ST

CR = within the clinical report
ST = as a supplementary table or figure
WT = as a working or CTRS table or figure
*=The tables and graphs listed above will also be done for the period from Dose 1 up to visit 5 and from dose 1 upto 2 weeks post dose 2 for the Total vaccinated cohort. The resulting tables will appear as supplement tables.

6.2.3. For Safety Analysis:

Table # in reference of Section 6.3	Table Title	Annexe analysis	Macro
Table R(A) 1	Percentage of subjects with SAE's classified by MedDRA system organ class during the study period (Total vaccinated cohort)	CR*	%UNSOL
Table R(A) 2	Percentage of subjects with AE's leading to drop out classified by MedDRA system organ class and Preferred Term during the study period (Total vaccinated cohort)	CR*	%UNSOL
Table R(A) 3	Listing of SAEs (Total vaccinated cohort)	ST*	%SAE
Table R(A) 4	Listings of fatalities from dose 1 of HRV or Placebo up to Visit 5 (Total vaccinated cohort)	ST*	
Table CTRS 1	Number (%) of subjects with serious adverse events (Total vaccinated cohort)	CTRS	%CTR_SAE
Table CTRS 3	Number (%) of subjects with adverse events (Total vaccinated cohort)	CTRS	%CTR_AE

*: a complementary analysis based on the ATP cohort for safety will be provided if more than 5% of the vaccinated subjects are excluded from that cohort. The resulting tables will appear as supplemental tables.

6.3. Template of tables for Annexe(A) analysis

The following tables/figures provide lay-out tables for the statistical analyses.

Table D(A) 1 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

See template for Table D 2

Table D(A) 2 Number of subjects at each visit and list of withdrawn subjects (Total vaccinated cohort)

Group	Visit	N	Withdrawn Subject	Reasons for withdraw
HRV	Visit1			
	Visit2			
	Visit3			
	Visit4			
	Visit5			
Placebo	Visit1			
	Visit2			
	Visit3			
	Visit4			
	Visit5			

N = number of subjects in each vaccine group

Table D(A) 3 Number of subjects entered, completed and withdrawn with reason for withdrawal at visit 4 (Total vaccinated cohort)

See template for Table D 5

Table D(A) 4 Number of subjects entered, completed and withdrawn with reason for withdrawal at visit 5 (Total vaccinated cohort)

See template for Table D 5

Table D(A) 5 Minimum and maximum activity dates (Total vaccinated cohort)

See template for Table D 8

Table D(A) 6 Summary of demographic characteristics (Total vaccinated cohort)

Characteristics	Parameters or Categories	HRV N= XXX		Placebo N= XXX		Total N= XXX	
		Value or n	%	Value or n	%	Value or n	%
Age(w) at dose 1 of HRV/placebo	Mean SD Median Minimum Maximum						
Age (w) at dose 2 of HRV/Placebo	Mean						
	SD						
	Median Maximum						
	Minimum						
Age (months) at visit 4 or at last contact if visit 4 not performed	Mean						
	SD						
	Median						
	Maximum						
	Minimum						
Age (months) at visit 5 or at last contact if visit 5 not performed	Mean						
	SD						
	Median						
	Maximum						
	Minimum						
Gender	Female Male						
Race	Black White/caucasian Oriental Arabic/north East/south east asian South asian American hispanic Japanese Other						

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(W)= age expressed in Weeks

Table D(A) 7 Summary of demographic characteristics (ATP cohort for Efficacy)

See template Table D(A) 6

Table D(A) 8 Subjects unblinded before database lock (date) (Total Vaccinated cohort)

See template for Table D 17

Table E(A) 1 Percentage of subjects with vaccine virus in gastroenteritis stool samples collected in case of GE episode from Dose 1 up to visit 5 (Total vaccinated cohort)

See template for Table E 1

Table E(A) 2 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 2 up to visit 4 - ATP cohort for efficacy

See template for

Table E 2

Table E(A) 3 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to visit 4- ATP cohort for efficacy

Category	HRV n	%	Placebo n	%	Total n	%
	N'=		N'=		N'=	
No stools collected Stools collected but no results available No stool results available						

N'= number of gastroenteritis episodes reported
n/%= number/percentage of GE episodes reported in the considered efficacy period within the specified category

Table E(A) 4 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to visit 4 by severity using the 20-point Vesikari scale - ATP cohort for efficacy

See template for Table E 3

Table E(A) 5 Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy

See template for Table E 4

Table E(A) 6 Percentage of subjects with severe RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy

See template for Table E 4

Table E(A) 7 Number of RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy

See template for Table E 6

Table E(A) 8 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by G and P type - ATP cohort for efficacy

See template for

Table E 7

Table E(A) 9 Characteristics (based on Vesikari scale) of severe RV GE episodes reported from 2 weeks after Dose 2 up to visit 4, by main RV types and overall - ATP cohort for efficacy

See template for Table E 8

Table E(A) 10 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 2 up to visit 4 – ATP cohort for efficacy

See template for Table E 9

Table E(A) 11 Percentage of subjects reporting any RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4 - ATP cohort for efficacy

See template for Table E 10

Table E(A) 12 Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4, by RV serotype - ATP cohort for efficacy

See template for

Table E 11

Table E(A) 13 Percentage of subjects reporting severe RV GE (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4 - ATP cohort for efficacy

See template for Table E 10

Table E(A) 14 Percentage of subjects reporting severe RV GE episode (Vesikari Score >=11) and efficacy of the vaccine from 2 weeks after Dose 2 up to visit 4, by RV serotype - ATP cohort for efficacy

See template for

Table E 11

Table E(A) 15 Percentage of subjects hospitalized due to RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP efficacy cohort

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV									
Placebo									

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
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases

Table E(A) 16 Percentage of subjects reporting all cause GE and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy

See template for Table E 10

Table E(A) 17 Percentage of subjects reporting all cause Severe GE and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy

See template for Table E 10

Table E(A) 18 Percentage of subjects hospitalized due to GE efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 4 - ATP cohort for efficacy

See template for Table E(A) 15

Table E(A) 19 Percentage of subjects reporting severe 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 - ATP cohort for efficacy

Severity using Vesikari scale	Group	N	n/N				Vaccine Efficacy			
			n	%	95%CI LL	UL	%	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
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases

Table E(A) 20 Efficacy of the vaccine against severe RV GE from 2 weeks after Dose 2 up to visit 5, by Cox - ATP cohort for efficacy

See template for Table E 15

Table E(A) 21 Efficacy of the vaccine against any RV GE from 2 weeks after Dose 2 up to visit 5, by Cox - ATP cohort for efficacy

See template for Table E 15

Table E(A) 22 Percentage of subjects reporting any and Severe RVGE episodes and risk difference of the vaccines from 2 weeks post dose 2 to visit 4 - ATP cohort for efficacy

See template for Table E 17

Figure E(A) 1 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to visit 4 – ATP cohort for efficacy

See template for Figure E 1

Figure E(A) 2 Efficacy of the vaccine against severe RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 2 up to Visit 4 – ATP cohort for efficacy

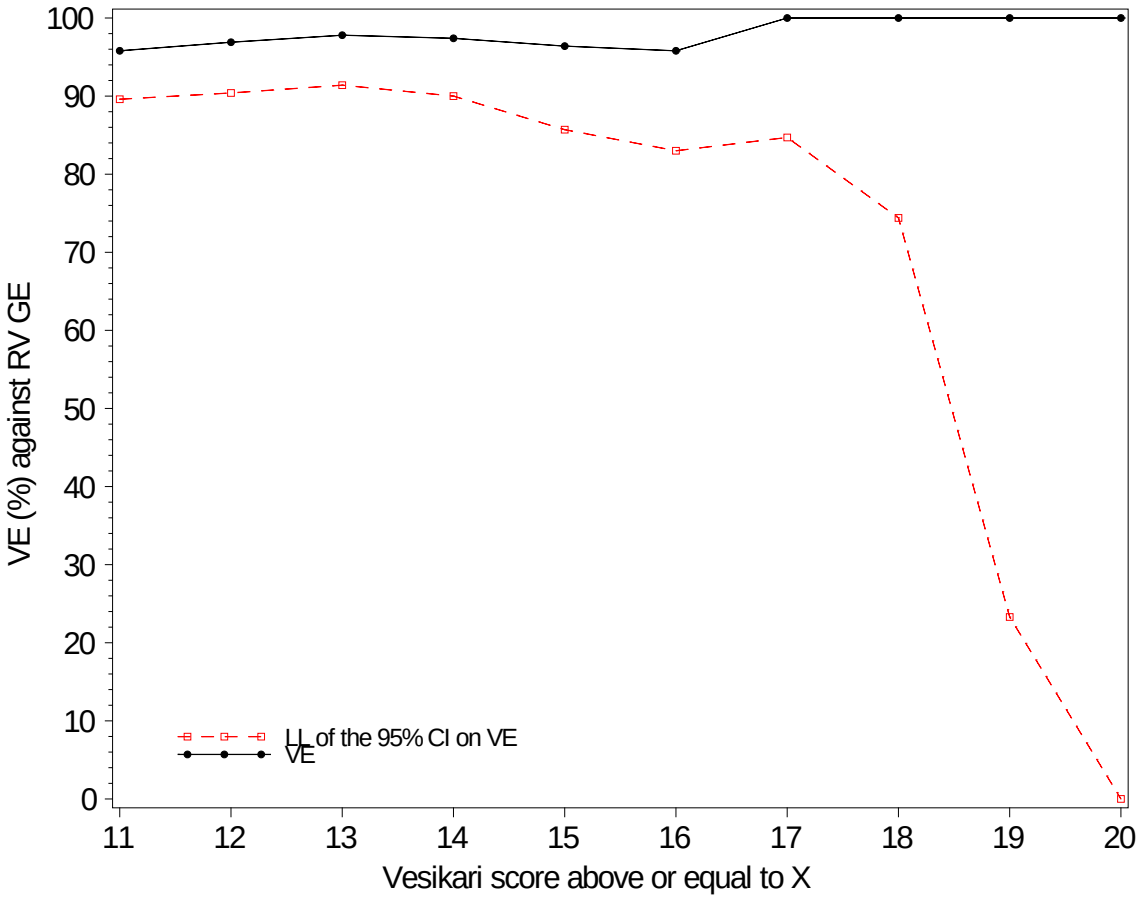


Figure E(A) 3 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to visit 5- ATP cohort for efficacy

See template for Figure E 2

Figure E(A) 4 The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to visit 5- ATP cohort for efficacy

See template for Figure E 2

Table R(A) 1 Percentage of subjects with SAE's classified by MedDRA system organ class during the study period (Total vaccinated cohort)

Primary System Organ	Preferred Term	HRV N=XX			Placebo N=XX			
Class (CODE)	(CODE)	n	%	95% CI	n	%	95% CI	
				LL UL			LL	UL
At least one symptom								
Gastrointestinal disorders (10017947)	Inguinal hernia (10022016)							
General disorders and administration site conditions (10018065)	Pain (10033371) Pyrexia (10037660)							
Infections and infestations (10021881)	Abscess (10000269) Bronchitis acute (10006452) Cellulitis (10007882) Furuncle (10017553) Gastroenteritis (10017888) Human herpesvirus 6 infection (10020431) Impetigo (10021531) Meningitis bacterial (10027202) Nasopharyngitis (10028810) Oral candidiasis (10030963) Pneumonia (10035664) Rhinitis (10039083) Skin infection (10040872) Upper respiratory tract infection (10046306) Viral infection (10047461)							
Injury, poisoning and procedural complications (10022117)	Fall (10016173)							
Musculoskeletal and connective tissue disorders (10028395)	Craniosynostosis (10049889)							
Nervous system disorders (10029205)	Convulsion (10010904) Somnolence (10041349)							
Psychiatric disorders (10037175)	Irritability (10022998)							
Respiratory, thoracic and mediastinal disorders (10038738)	Rhinitis allergic (10039085)							
Skin and subcutaneous tissue disorders (10040785)	Dermatitis diaper (10012444) Intertrigo (10022622) Rash maculo-papular (10037868)							

At least one symptom = At east one symptom experienced regardless of the System Organ Class
N = Number of subjects having received at least one dose
n/% = Number / percentage of subjects reporting at least once a specified symptom within 31 days after vaccination day 0 to day 30

95% CI = Exact 95% confidence interval

Table R(A) 2 Percentage of subjects with AE's leading to drop out classified by MedDRA system organ class and Preferred Term during the study period (Total vaccinated cohort)

See template for

Table R(A) 2

Table R(A) 3 Listing of SAEs (Total vaccinated cohort)

Group	Pid	Case Id	Age (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
HRV													
Placebo													

Age (Week) = Age (Week) at SAE onset

Table R(A) 4 Listings of fatalities from dose 1 of HRV or Placebo up to Visit 5 (Total vaccinated cohort)

Group	dose	Day since last dose	Pid	Case Id	Sex	Day since dose 1	date of death	Age at death (days)	Treatment	Verbatim

Table CTRS 1 Demography for CTRS

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 (%)		
Withdrawn for other reasons, n (%)		
Demographics	HRV	Placebo
N (Total Vaccinated Cohort)		
Females:Males		
Mean Age, months (SD)		
White/caucasian, n (%)		

Table CTRS 2 Number (%) of subjects with serious adverse events (Total vaccinated 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 CTRS 3 Number (%) of subjects with adverse events (Total vaccinated cohort)

Most frequent adverse events - On-Therapy (occuring between day 0-30 following vaccination)	HRV N =	Placebo N =
Subjects with any AE(s), n(%)		
Rhinitis		
Nervousness		
Fever		
upper resp tract infection		
Conjunctivitis		
Coughing		
otitis media		
Gastroesophageal reflux		
Flatulence		
Fatigue		
abdominal pain		
crying abnormal		
tooth ache		

7. ANNEX 1: CRITERIA FOR ELIMINATING SUBJECTS FROM STAT ANALYSES

Refer to RAP - Elimination code specifications Form

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 III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study: 107625 (Rota-056) Development Phase: III

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] M.B.B.S

Title of Sponsor Signatory: Director, Rotavirus vaccines
Global Clinical Research and Development
GlaxoSmithKline Biologicals

Signature: [redacted]

Date: Oct 21, [redacted]09

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Global Clinical Research and Development
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Please note that by signing this page, you take responsibility for the content of the clinical study report, including appendices

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study: 107625 (Rota-056) Development Phase: III

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: Dr. [redacted]

Title of Sponsor Signatory: Deputy Director, Clinical Development, GlaxoSmithKline K.K.

Signature: [redacted]

Date: 29. Oct. 2009

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GlaxoSmithKline Biologicals

Study title

Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.

Study detailed title

A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Annex Clinical Study Report for Study 107625 (Rota-056)

(Development Phase III)

Indication Studied: Primary immunisation of healthy infants against rotavirus disease/illness

Study initiation date:	19 June 2007
Study completion date:	21 November 2009
Date of database freezing:	01 March 2010
Date of annex report:	12 April 2010
Earlier Study Report: (Primary Study Report)	25 September 2009
Report Scope:	This annex report presents final efficacy analyses during the efficacy follow-up periods starting from 2 weeks post Dose 2 up to Visit 5, from 2 weeks post Dose 2 up to Visit 4 and from Visit 4 to Visit 5. In addition, safety data (serious adverse events and adverse events leading to drop out) collected during the entire course of the study is also presented.

Sponsor Signatories: [redacted] M.B.B.S
Director, Rotavirus vaccines
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GlaxoSmithKline Biologicals

Dr. [redacted]
Deputy Director, Clinical Development,
GlaxoSmithKline K.K.

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

SYNOPSIS

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 III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Principal investigator: This study was conducted by several principal investigators. Dr. [redacted] was involved in reviewing and approving the study report on behalf of all other investigators.

Study centres: This study was conducted at 20 centres in Japan.

Publication (reference): Not published as of 12 April 2010

Study period: Study initiation date: 19 June 2007 Study completion date: 21 November 2009 Date of database freezing: 01 March 2010	**Clinical phase:** III

Objectives: The study objectives considered for analyses presented in this annex study report are listed below.

Primary:

- To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary:

Efficacy

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety*

- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

*Blinded results for unsolicited AEs (31 days after each dose) were presented in the study report 107625 (Rota-056) and unblinded results for unsolicited AEs (31 days after each dose) are included in this annex report.

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 design: Randomised, double-blind, placebo-controlled and multi-centre study with 2 parallel groups: Group HRV lyophilised vaccine (also referred to as HRV group) and Group Placebo. Routine childhood vaccinations were administered as per local practice. There was active follow-up for the occurrence of gastroenteritis (GE) episodes leading to medical intervention via telephone contact or other means for the entire study period (from Dose 1 up to two years of age). This annex report presents the efficacy and safety results up to two years of age.

Number of subjects:	Total	HRV Group	Placebo group
Enrolled and vaccinated	765	508	257
Completed Visit 5	717	476	241
According-To-Protocol (ATP) cohort for Efficacy – efficacy period from 2 weeks post Dose 2 up to Visit 4/ efficacy period from 2 weeks post Dose 2 up to Visit 5	748	498	250
ATP cohort for efficacy – efficacy period from Visit 4 up to Visit 5	730	487	243

Diagnosis and criteria for inclusion: Healthy infants, born after a gestation period of 36 – 42 weeks (inclusive), between and including 6 – 14 weeks (42 – 104 days) of age at the time of the first dose of the HRV vaccine/placebo. Written informed consent was obtained from the parent or guardian of each subject before any study-specific procedures were performed.

Study vaccine, dose, mode of administration, lot no.: Refer to the Study Report 107625 (Rota-056) for details on the study vaccine, dose, mode of administration and lot no.

Reference vaccine /Comparator, dose and mode of administration, lot no.: Refer to the Study Report 107625 (Rota-056) for details on the reference vaccine, dose, mode of administration and lot no.

Duration of study: The duration of the study from Visit 1 up to Visit 5 was approximately 2 years.

Criteria for evaluation of efficacy: For each GE episode leading to medical intervention occurring during the study period, a GE diary card was completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE leading to medical intervention was recorded on the same card. Intensity of the GE episodes was scored using the 20-point Vesikari scoring system, with score ≥11 points considered as severe. Available stool samples collected during each GE episode leading to medical intervention from Visit 1 up to Visit 5 were tested at GSK Biologicals using Enzyme Linked immunosorbent assay (ELISA) to detect RV. If positive, the sample was tested by polymerase chain reaction (PCR) to determine the G and the P types. If any G1 RV was detected, vaccine virus was differentiated from the wild type strain by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by reverse hybridisation assay or an equivalent approach.
The study endpoints considered for analyses presented in this annex study report are listed below.

Primary Endpoint:

- Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary Endpoints:

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the 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)

- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Criteria for evaluation of Safety: Recording of unsolicited AEs occurring during the 31-day (Day 0 – Day 30) follow-up period after each dose. Recording of AEs (serious and non-serious) leading to drop-out throughout the study period and recording of serious adverse events (SAEs) occurring during the entire study period up to Visit 5.
The study endpoints considered for analyses presented in this annex study report are listed below.
Secondary Endpoint:

- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Statistical methods:
Analysis of demography: The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall. The median, mean, range and standard deviation of age in months at Visit 4 and Visit 5 or at last contact if the study visit was not performed was also calculated per group and overall. The racial and gender composition per group was presented.

Analysis of Efficacy: The duration of the efficacy follow-up period was summarised by group. The percentages of subjects with any and severe RV GE (overall and by RV type) leading to medical intervention from 2 weeks after Dose 2 up to Visit 5 were calculated with their 95% Confidence Interval (CI) and compared between groups. The vaccine efficacy for each efficacy endpoint was calculated with its 95% CI. The primary objective was reached if the lower limit of the 95% CI on vaccine efficacy (conditional method) for the HRV group against any RV GE requiring medical intervention caused by wild-type RV strains during the efficacy follow-up period was > 0%. Additional supportive and exploratory analyses were performed (i.e. efficacy against GE of any aetiology leading to a medical intervention). An exploratory analysis was performed for vaccine efficacy against any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains by Cox method. Additional analyses on vaccine efficacy against hospitalisation due to GE of any aetiology and vaccine efficacy during the period starting from 2 weeks post Dose 2 up to Visit 4 were performed.
Similar analyses were performed for the efficacy period starting from 2 weeks post Dose 2 up to Visit 4 and from Visit 4 to Visit 5.

Analysis of Safety: The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0 – Day 30) follow-up period after any doses with its exact 95% CI was tabulated by group, by System Organ Class (SOC) and Preferred term (PT). Similar tabulation was done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and for AEs leading to drop out. Serious adverse events reported during the study period (i.e. from Dose 1 up to Visit 5) were described in detail. The percentage of subjects with SAEs reported during the study period was tabulated by group according to MedDRA SOC and PT classification, with its exact 95% CI. The percentage of subjects with adverse events (serious and non-serious) leading to the withdrawal from the study with its exact 95% CI was tabulated by group, by SOC and PT.

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)

Summary:

Demography Results: In the ATP cohort for efficacy, the mean age was 7.7 weeks (range: 6 to 14 weeks) at Dose 1 of HRV vaccine/placebo, 12.7 weeks (range: 10 to 20 weeks) at Dose 2 of HRV vaccine/placebo, 11.4 months (range: 4 to 13 months) at Visit 4 or at last contact if Visit 4 was not performed and 23 months (range: 4 to 25 months) at Visit 5 or at last contact if Visit 5 was not performed. All the subjects were of Japanese origin; 47.6% of subjects were female and 52.4% of subjects were male.

Efficacy Results: Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) and the total vaccinated cohort. The mean duration of the efficacy follow-up (from 2 weeks post Dose 2 up to Visit 5) was 1.68 years in the HRV group and 1.67 years in the placebo group.

Primary Endpoint:

- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (2.8% versus 13.6%; p-value <0.001) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against any RV GE episodes leading to medical intervention caused by the circulating wild-type RV was 79.3% [95% CI: 60.5%; 89.8%]. The primary objective of the study was reached since the lower limit of the 95% CI on vaccine efficacy was >0% (criteria specified for fulfilling the primary efficacy objective).

Secondary Endpoints:

- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (0.4% versus 4.8%; p-value <0.001) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against severe RV GE leading to medical intervention caused by circulating wild-type RV was 91.6% [95% CI: 62.4%; 99.1%].
- The percentage of subjects with report of any RV GE leading to medical intervention caused by G1 wild type in the HRV group was significantly lower compared to the placebo group (0.8% versus 5.2%; p-value <0.001) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against any RV GE episodes caused by G1 wild type leading to medical intervention was 84.6% [95% CI: 50.0%; 96.3%].
- When considering all isolated non-G1 types (G2, G3, G4 and G9), significantly fewer subjects in the HRV group reported any RV GE leading to medical intervention compared to the placebo group (2.0% versus 8.4%; p-value <0.001) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against any RV GE caused by non-G1 types leading to medical intervention was 76.1% [95% CI: 47.0%; 89.9%].
- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by G1 wild-type compared to the placebo group (0.2% versus 2.4%; p-value 0.014) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against severe RV GE caused by G1 wild-type RV leading to medical intervention was 91.6% [95% CI: 31.0%; 99.8%].

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)

- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by non-G1 types compared to the placebo group (0.2% versus 2.4%; p-value 0.014) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against severe RV GE caused by non-G1 type was 91.6% [95% CI: 31.0%; 99.8%].
- There were very few reports of hospitalisation due to RV GE (1 subject in the HRV group and 2 subjects in the placebo group).
- During the period starting from Dose 1 up to Visit 5, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 80.3% [95% CI: 62.6%; 90.2%] and 92.2% [95% CI: 65.6%; 99.1%], respectively.

Table 1: Vaccine efficacy from 2 weeks post Dose 2 up to Visit 5 (ATP Cohort for efficacy)

			n/N			VE			
				95% CI			95% CI		
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
Any RV GE due to circulating wild-type RV leading to medical intervention (Primary efficacy endpoint)									
HRV	498	14	2.8	1.5	4.7	79.3	60.5	89.8	<0.001
Placebo	250	34	13.6	9.6	18.5	-	-	-	-
Severe RV GE due to circulating wild-type RV leading to medical intervention*									
HRV	498	2	0.4	0.0	1.4	91.6	62.4	99.1	<0.001
Placebo	250	12	4.8	2.5	8.2	-	-	-	-
Any RV GE due to wild-type G1									
HRV	498	4	0.8	0.2	2.0	84.6	50.0	96.3	<0.001
Placebo	250	13	5.2	2.8	8.7	-	-	-	-
Severe RV GE due to wild-type G1*									
HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
Placebo	250	6	2.4	0.9	5.2	-	-	-	-
Any RV GE due to non-G1 types									
HRV	498	10	2.0	1.0	3.7	76.1	47.0	89.9	<0.001
Placebo	250	21	8.4	5.3	12.6	-	-	-	-
Severe RV GE due to non-G1 types*									
HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
Placebo	250	6	2.4	0.9	5.2	-	-	-	-
Hospitalisation due to RV GE									
HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
Placebo	250	2	0.8	0.1	2.9	-	-	-	-

HRV = HRV group; Placebo = Placebo group; Notes: *episodes with score ≥ 11 points on Vesikari scale; N = number of subjects included in each group; n = number of subjects reporting at least one event in each group; P-value = Two sided Exact P-value conditional to number of cases; VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 95 % Lower and Upper confidence limits

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 Results: The safety analyses were performed on the total vaccinated cohort.

- The percentage of subjects with report of at least one unsolicited AE classified by MedDRA SOC and PT was 54.9% in the HRV group and 56.0% in the placebo group.
- During the entire study period, at least one SAE was reported for 14.2% of subjects in the HRV group and for 17.1% of subjects in the placebo group. None of the SAEs were considered by the investigator to be causally related to vaccination.
- There were no fatal events reported in this study.
- There was no significant safety data received after the database freeze date for this study.

Withdrawals due to adverse events /serious adverse events:

- [redacted] This medical condition developed 20 days after receiving Dose 2 and the randomisation code was broken. The SAE was not considered by the investigator to be causally related to vaccination. Hepatic insufficiency was caused by neonatal intrahepatic cholestasis due to Citrin deficiency. This SAE was ongoing at the time of study end.
- [redacted] This subject experienced the AE 38 days after receiving Dose 2 of placebo. The AE lasted only for a day and the subject was withdrawn from the study after Visit 3. The AE was not considered by the investigator to be causally related to vaccination.

Conclusions:

Efficacy:

- Two doses of the HRV vaccine were found to be highly effective against any RV GE caused by wild-type RV leading to medical intervention during the efficacy period starting from 2 weeks post Dose 2 up to Visit 5 with a vaccine efficacy of 79.3% [95% CI: 60.5%; 89.8%] thereby meeting the primary objective of the study.
- Two doses of HRV vaccine were found to be highly efficacious against:
- Severe RV GE caused by the circulating wild-type RV leading to medical intervention with a vaccine efficacy of 91.6% [95% CI: 62.4%; 99.1%].
- Any RV GE episodes caused by G1 wild-type RV leading to medical intervention with a vaccine efficacy of 84.6% [95% CI: 50.0%; 96.3%].
  - Severe RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
  - Any RV GE leading to medical intervention caused by non-G1 RV type with a vaccine efficacy of 76.1% [95% CI: 47.0%; 89.9%].
  - Severe RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
  - There were very few reports of hospitalisation due to RV GE leading to medical intervention (1 subject in the HRV group and 2 subjects in the placebo group).
- During the period starting from Dose 1 up to Visit 5, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 80.3% [95% CI: 62.6%; 90.2%] and 92.2% [95% CI: 65.6%; 99.1%], respectively.

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:

- The incidence of unsolicited symptoms was similar in the HRV group and placebo group.
- There was no evidence of a clinically meaningful difference between the HRV group and placebo group for SAEs reported from Dose 1 up to Visit 5.

Date of annex report: 12 April 2010

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LIST OF TABLES

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LIST OF SUPPLEMENTS

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
BCG	Bacille Calmette-Guérin
CI	Confidence Interval
DTPa	Diphtheria and tetanus toxoids and acellular pertussis
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
GE	Gastroenteritis
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase Chain Reaction
PT	Preferred Term
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious adverse event
SMS	Short Message Service
SOC	System Organ Class

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 was 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 are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. 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. 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.
Completed:	Subjects who completed the last study visit.
Diarrhoea:	Passage of three or more looser than normal stools within a day.
Diary card:	Cards given to the parents /guardians by the investigator to record adverse events following vaccination.
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.
Gastroenteritis:	Diarrhoea with or without vomiting.
Medical intervention:	Defined as medical doctor visit, an emergency room visit or hospitalisation.
RV GE for primary efficacy analysis:	An episode of any GE leading to a medical intervention occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample

	collected as soon as possible after the start of the episode.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system).
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subject(s):	Term used throughout the protocol 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.
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 was 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, amendment, the informed consent, and other information that required pre-approval were reviewed and approved by each investigational centre IRB.

1.2. Ethical conduct of the study

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

1.3. Subject information and consent

Written informed consent was obtained from each parent/guardian prior to the performance of any study-specific procedures. Electronic case report forms were provided for each subject's data to be recorded.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

2.1. Administrative structure

This study was conducted at 20 centres in Japan by several principal investigators. Dr. [redacted] was involved in reviewing and approving the study report on behalf of the other investigators.

GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium was the study sponsor and was responsible for administrative aspects 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 HRV vaccine clinical development. In this capacity, the IDMC periodically reviewed all Serious Adverse Events (SAEs) reported during this study till 31 December 2007. IDMC was dissolved on 18 February 2008.

3. INTRODUCTION

Rotaviruses (RV) are the leading cause of severe diarrhoea among young children <5 years of age throughout the world. A recent review estimated that RV is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year where the majority of the deaths occur in low-income countries [WHO, 2009]. In developed countries, RV infection rarely results in death but RV remains the most common cause of hospitalization for gastroenteritis (GE) in children and leads to major medical and societal costs [Glass, 1996]. In a hospital based study in Japan, RV was detected in approximately 58% of children aged less than 5 years who were hospitalised for acute GE. Majority of the cases (39%) were reported during the second year of life and 89% of the cases had occurred by 36 months of age. Thus, introducing a vaccine may help in reducing the substantial disease burden associated with RV GE in Japan [Nakagomi, 2005].

This study was undertaken to provide the Regulatory Authorities in Japan with immunogenicity, efficacy, safety and reactogenicity data for GSK Biologicals' HRV vaccine when used in Japanese infants aged approximately 2 months at the time of the first dose. The study was designed to evaluate the efficacy of the HRV vaccine when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest. The study report 107625 (Rota-056) presented final analysis of efficacy, reactogenicity, safety and immunogenicity data of all subjects up to the data lock point of 31 March 2009 (when the target of at least 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached).

During the period starting from 2 weeks post Dose 2 up to the data lock point of 31 March 2009, vaccine efficacy against any RV GE leading to medical intervention caused by the circulating wild-type RV was 81.9% [95% CI: 60.0%; 92.6%]. The primary objective of the study was reached since the lower limit of the 95% CI on vaccine efficacy was >0% (criteria specified for fulfilling the primary efficacy objective). Vaccine efficacy against severe RV GE leading to medical intervention caused by circulating wild-type RV was 95.4% [95% CI: 68.6%; 99.9%]. Vaccine efficacy against any RV GE caused by G1 wild-type leading to medical intervention was 91.6% [95% CI: 31.0%; 99.8%]. Vaccine efficacy against severe RV GE caused by G1 wild-type RV leading to medical intervention was 100% [95% CI: 24.0%; 100.0%].

This annex report presents the efficacy and safety data up to two years of age (i.e. Visit 5).

4. STUDY OBJECTIVES

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

4.1. Primary objective

- To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

See Section 5.11.1 for the primary endpoint.

4.2. Secondary objectives

Efficacy

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety*

- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

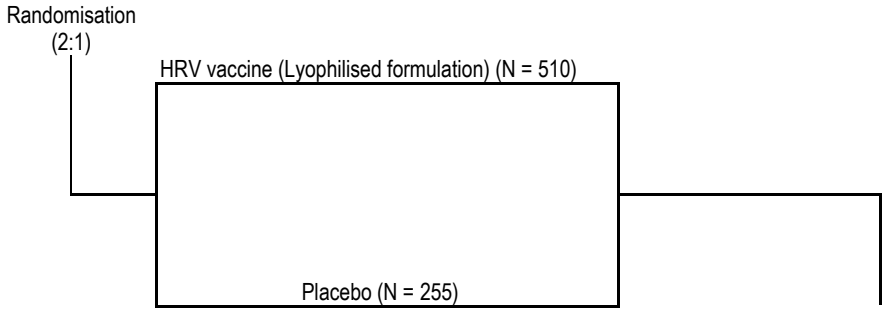
*Blinded results for unsolicited AEs (31 days after each dose) were presented in the study report 107625 (Rota-056) and unblinded results for unsolicited AEs (31 days after each dose) are included in this annex report.

See Section 5.11.2 for the secondary endpoints.

5. INVESTIGATIONAL PLAN

5.1. Study design

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



	Vaccination Visits			Safety and efficacy follow-up Visits	
	Visit 1	Visit 2	Visit 3	Visit 4#	Visit 5#
	Dose 1	Dose 2			
	Day 0	Month 1	Month 2		
Age:	6 – 14 weeks			1 year	2 years
	Blood sampling*		Blood sampling*		

N: Number of subjects planned to be enrolled.
HRV: Human rotavirus
*: Blood sampling in the immunogenicity subset (N = 60)
#: Safety and efficacy follow-up visits.

5.1.1. Overall study design – Description

- Experimental design: Phase III, randomised, double-blind, placebo-controlled, multicenter study in Japan with two parallel groups.
- Treatment allocation: Randomised (2:1 ratio).
- Blinding: Double-blind.
- Treatment Groups:
  - Group HRV lyophilised vaccine (also referred to as HRV group) (N = 510)
  - Group Placebo (N = 255)
- Vaccination schedule: Vaccination according to 0, 1 month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks (42–104 days) at the time of the first dose.
- Control: Placebo.

- Routine childhood vaccination according to local practice could be administered concurrently with the study vaccinations as recommended in Japan. All vaccines administered from birth up to Visit 3 were to be documented in the electronic case report form (eCRF).
- During the entire study period (from Dose 1 up to Visit 5 [two years of age]), active follow-up for occurrence of GE episodes (diarrhoea) leading to medical intervention via telephone contact or other means (at least every two weeks).
- For each GE episode leading to medical intervention occurring during the study period,
  - a GE diary card was to be completed daily until end of the GE symptoms.
  - a stool sample was to be collected as soon as possible after symptoms began but preferably not later than 7 days after the onset of GE symptoms.
- Recording of SAEs throughout the study period.
- Type of study: Self-contained.
- Data collection: Remote Data Entry (RDE).
- Five scheduled visits per subject: at Months 0, 1, 2 and at one and two years of age.
- Duration of the study: The intended duration of the study, per subject was till the subject was two years of age

5.2. Study procedures

5.2.1. Outline of study procedures

Table 1 presents the outline of study procedures.

Table 1 List of study procedures

Age	6-14 weeks			One year	Two years
Visits Timing Sampling time point	VISIT 1 Day 0 Pre-vacc	VISIT 2 Month 1	VISIT 3 Month 2 Post-vacc 2	VISIT 4	VISIT 5
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	●	●	-	-	-
Randomisation	●	-	-	-	-
Blood sampling (1 ml) for antibody determination in an immunogenicity subset *	●	-	●	-	-
Study vaccination (HRV vaccine/ Placebo)	●	●	-	-	-
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians	●	●	-	-	-
Return of reactogenicity diary card	-	○	○	-	-
Transcription of the reactogenicity diary card		●	●	-	-
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●	-	-
Record any concomitant medication/vaccination, by investigator	●	●	●	●#	●#
Recording of GE leading to medical intervention occurring throughout the study period	●	●	●	●	●
Contact the subject's parent/guardian to check GE occurrence at least every two weeks	○	○	○	○	○
Collection of stool samples if subject has GE leading to medical intervention	●	●	●	●	●
Return of GE diary card	-	○	○	○	○
GE diary card transcription	-	●	●	●	●
Recording of SAEs	●	●	●	●	●
Reporting AEs leading to drop-out	●	●	●	●	●
Conclusion at Visit 4				●	
Study conclusion	-	-	-	-	●

Note: Final analyses was done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or when all subjects had reached two years of age, whichever was the earliest.

● was used to indicate a study procedure that required documentation in the individual eCRF.

○ was used to indicate a study procedure that does not require documentation in the individual eCRF.

*Blood sampling was done only from subjects in the immunogenicity subset (N = 60).

for concomitant medication administered for the treatment of an AE leading to drop-out/SAE.

5.2.2. Intervals between study visits

The intervals between study visits are presented in Table 2.

Table 2 Intervals between study visits

Interval /Visit	Range of interval /Visit	Length of Adapted Interval
Visit 1→Visit 2	30 – 48 days	21 – 48 days
Visit 2→Visit 3	30 – 48 days	21 – 48 days
Visit 4	1 year of age ± 15 days	-
Visit 5	2 years of age ± 15 days	-

N.B: The reference date for intervals between study visits: the first vaccination date.

5.3. Selection of study population

Target enrolment was 765 subjects (510 subjects in HRV lyophilised vaccine group and 255 subjects in the placebo group). All subjects were enrolled at multiple sites in Japan. Refer to Study Report 107625 (Rota-056) for the eligibility criteria to be satisfied by the subjects at study entry and for contraindication to subsequent dose of the study vaccine.

5.3.1. Elimination criteria

The following criteria were to be 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 determined a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 5.11.4 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids were allowed).
- Administration of immunoglobulin 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 returned for the concluding visit (Visit 5) foreseen in the protocol was considered to have completed the study.

5.3.2.2. Subject Withdrawal

Subjects who were withdrawn because of AEs were clearly distinguished from subjects who were withdrawn for other reasons. Investigators followed subjects who were withdrawn as result of a SAE/AE until resolution of the event.

Withdrawals were not replaced.

5.3.2.3. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study was any subject who did not come back for the concluding visit (Visit 5)/was not available for the concluding contact foreseen in the protocol.

A subject qualified as a 'withdrawal' from the study when no study procedure had occurred, no follow-up had been performed and no further information had been collected for this subject from the date of withdrawal/last contact.

Investigators made an attempt to contact those subjects who did not return for scheduled visits or follow-up.

Information relative to the withdrawal was to be documented on the Study Conclusion page of the eCRF. The investigator was to 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 (was to be specified)
- consent withdrawal, not due to an adverse event
- moved from the study area
- lost to follow-up
- other (was to be specified).

5.3.2.4. Subject withdrawal from administration of the investigational product

A 'withdrawal' from the investigational product was any subject who did not receive the complete treatment, i.e. when no further planned dose was 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 have been performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational product was to be documented on the Vaccine Administration page of the eCRF. The investigator was to 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 (was to be specified).

5.4. Composition and administration of vaccines

Refer to Study Report 107625 (Rota-056) for details on the vaccine composition, vaccine administration, lot numbers, and dosage of the vaccines administered in this study.

5.4.1. Treatment allocation and randomization

Target enrolment was 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the placebo group) to obtain 612 evaluable subjects (408 subjects in the HRV group and 204 subjects in the placebo group) for the evaluation of the primary objective.

The actual treatment number used for first vaccination of the subject was to be recorded by the investigator in the eCRF (Randomisation/Treatment Allocation Section).

Refer to Study Report 107625 (Rota-056) for details on randomization.

5.4.2. Blinding

The study was conducted in a double-blind manner with respect to HRV vaccine and placebo. The parents/guardians of the subjects, the study personnel and the investigator were unaware of the study vaccine administered (HRV vaccine or placebo). Blinding was maintained for the whole study period. Since the final analysis was done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains was reached during the efficacy follow-up period, access to the individual treatment decode during the final analysis was limited to an external statistician and the database administrator to maintain double blinding until study end. This allowed unbiased evaluation of the study vaccine.

The investigator, or person designated by the investigator, contacted GSK Biologicals' Central Safety physician directly or via the local safety contact to discuss the need for emergency unblinding. The GSK Biologicals' Central Safety Office accessed the individual randomization code. The code was broken by the GSK Biologicals' Central Safety physician 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.

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) was to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which was unexpected and

attributable/suspected, prior to regulatory reporting. The Clinical Safety physician was responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs.

5.5. Prior and concomitant medication/vaccinations

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

Any investigational medication or vaccine administered throughout the study was recorded in the eCRF.

Refer to Study Report 107625 (Rota-056) for details on prior and concomitant medication/vaccinations administered during the study.

5.6. Assessment of efficacy variables

Active follow-up for occurrence of GE leading to medical intervention was conducted during the period starting from administration of Dose 1 up to the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or Placebo until end of study visit (i.e. Visit 5), the intention was to make contact with each subject's parent/guardian at least once every two weeks to check on the occurrence of any GE leading to medical intervention. This contact was by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or health care workers or other convenient means. All contacts were logged. In case of unavailability of subject’s parent/guardian at the time of contact, at least one more attempt was made before the next planned contact.

For each GE episode leading to medical intervention occurring during the study period, a GE diary card was completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE leading to medical intervention was recorded on the same card. The completed diary cards were returned to the investigator at the following study visit.

Data Collection for GE cases leading to medical intervention

Any GE episode (defined as diarrhoea with or without vomiting) leading to a medical intervention starting from Visit 1 to study end was to be documented using the GE diary card. The following information was to be collected on the GE diary card during each GE episode: Axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given.

Medical attention (medical doctor visit, emergency room visit or hospitalisation) was also recorded for each GE episode.

Vesikari scale to assess intensity of GE episodes leading to medical intervention

The information collected on the GE diary card allowed the assessment of the intensity of each GE episode using a 20-point scoring system.

In the 20-point scoring system, points were assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy or hospitalisation for each episode of GE leading to medical intervention as shown in Table 3.

Table 3 The 20-point scoring system to determine the intensity of GE episodes leading to medical intervention reported during the study

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

* The highest temperature recorded during the episode was scored.

A score < 7 was prospectively defined as mild, a score 7 - 10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe.

Periodic contact was made with the subjects' family to enquire about the occurrence of GE leading to a medical intervention. Collection of a stool sample was requested if not yet provided and if GE occurred since last contact. For a GE considered to be an SAE, the SAE screen/form in the eCRF was completed.

Collection of stool samples during GE leading to medical intervention

Parents/guardians were instructed to collect stool sample(s) from the subject if the subject developed GE leading to medical intervention during the entire study period. A stool sample was to be collected as soon as possible after illness began. A stool sample was to

be collected for each GE episode leading to medical intervention. A second stool sample was to be collected if the first sample was insufficient. Two occurrences of GE were classified as separate episodes, if there were 5 or more diarrhoea-free days between the episodes.

Analysis of stool samples during GE leading to medical intervention

Available stool samples collected during each GE episode leading to medical intervention from Visit 1 up to Visit 5 were tested at GSK Biologicals using Enzyme Linked immunosorbent assay (ELISA) to detect RV. If positive, the sample was tested by polymerase chain reaction (PCR) to determine the G and the P types. If any G1 RV was detected, vaccine virus was differentiated from the wild type RV by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) followed by reverse hybridisation assay or an equivalent approach.

5.7. Laboratory assays and time points

Refer to Study Report 107625 (Rota-056) for details on the laboratory assays.

5.8. Assessment of immunogenicity variables

Refer to Study Report 107625 (Rota-056) for details on the assessment of immunogenicity variables.

5.9. Assessment of safety variables

5.9.1. Adverse events

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.

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 was evaluated by the investigator. As a consistent method of soliciting AEs, the subject’s parent/guardian was 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. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination were established.

Investigators followed-up subjects:

- with SAEs or subjects withdrawn from the study as a result of an AE, until the event had resolved, subsided, stabilised, disappeared, the event was otherwise explained, or the subject was lost to follow-up;
- or, in the case of other non-serious AEs, until they completed the study or they were lost to follow-up.

When an AE/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 an AE/SAE 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. vital signs) 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 5.9.1 SAE, as defined in Section 5.9.2. 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that were present or detected at the start of the study and did not worsen, were not 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.

The intensity of each AE and SAE recorded in the eCRF or SAE Report Form, as applicable, was assigned to one of the following categories:

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, have prevented attendance at school/kindergarten/a day-care centre and caused the parents/guardians to seek medical advice.)

An AE that was assessed as grade 3 (severe) was not necessarily the same as a SAE. Grade 3 was a category utilised for rating the intensity of an event; and both AEs and SAEs could be assessed as grade 3. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in Section 5.9.2.

Assessment of causality

The investigator was obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator used 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 was considered and investigated. The investigator also consulted the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

In case of concomitant administration of multiple vaccines, it may not have been possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator, therefore should have assessed whether the AE was causally related to vaccination rather than to the individual vaccines.

Causality of all other AEs was assessed by the investigator using the following question:

"Was there a reasonable possibility that the AE (or SAE) may have been caused by the investigational product?"

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

Non-serious and serious AEs were evaluated as two distinct events. If an event met the criteria to be determined "serious", it was examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine, if applicable
- Erroneous administration
- Other cause (was to be specified).

Assessment of Outcome

Outcome of any non-serious AE or any SAE reported during the entire study were assessed as:

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

5.9.2. Serious adverse events

A serious adverse event (SAE) was any untoward medical occurrence that:

a. resulted in death,

b. was life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' referred to an event in which the subject was at risk of death at the time of the event. It did not refer to an event, which hypothetically might have caused death, if it were more severe.

c. required hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation signified that the subject was 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 occurred during hospitalisation were AEs. If a complication prolonged hospitalisation or fulfilled any other serious criteria, the event was serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE was considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE.

d. resulted in disability/incapacity, or

NOTE: The term disability meant a substantial disruption of a person's ability to conduct normal life functions. This definition was 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 have interfered or prevented everyday life functions but did not constitute a substantial disruption.

e. 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 that may not have been immediately life-threatening or resulted in death or hospitalisation but may have

jeopardised the subject or may have required 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 did not result in hospitalisation.

The standard time period for collecting and recording SAEs began at randomisation or the first receipt of the HRV vaccine/Placebo and ended at the last study visit (i.e. Visit 5) following administration of the last dose of the HRV vaccine/Placebo for each subject.

The investigator inquired about the occurrence of AEs/SAEs at every visit/contact during the study and throughout the follow-up phase as appropriate.

GSK Biologicals may have requested the investigator to 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 was then obliged to assist. If a subject died during participation in the study or during a recognised follow-up period, GSK Biologicals was to be provided with a copy of any available post-mortem findings, including histopathology.

5.10. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, case report form and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the Company representative(s) prior to study start. A multi-investigator meeting was held prior to the 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 CRF/eCRF completion. All procedures were performed according to methodologies detailed in GlaxoSmithKline Biologicals Standard Operating Procedures (SOPs).

Independent Audit statement:

- This study was subject to audit by GlaxoSmithKline's department of Worldwide Regulatory Compliance-GCP (WRC-GCP).
- This study was subject to audit by GlaxoSmithKline's Regulatory Compliance in Japan.

5.11. Statistical methods

All statistical analyses were performed using SAS 9.1 and Proc StatXact-7.

Analyses were performed according to the protocol and the study Reporting and Analysis Plan (RAP). Refer to Section 5.12.2 for changes to analyses specified in the protocol.

The study endpoints considered for analyses presented in this annex study report are listed below.

5.11.1. Primary endpoint

- Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

5.11.2. Secondary endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety

- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Refer to the study protocol for all study endpoints.

5.11.3. Determination of sample size

Refer to the Study Report 107625 (Rota-056) for details on sample size estimation.

5.11.4. Study cohorts /data sets analyzed

5.11.4.1. Total Vaccinated cohort

The total vaccinated cohort included all subjects with at least one 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.

5.11.4.2. ATP cohort for efficacy

The ATP cohort for efficacy included all subjects:

- who received two doses of HRV vaccine or placebo,
- who entered the efficacy surveillance period:
  - had follow-up beyond 2 weeks after Dose 2 of study vaccination,
- who had no rotavirus other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks after Dose 2 of HRV vaccine or placebo,
- for whom the randomisation code was not broken,
- who did not receive a vaccine forbidden by or not specified in the protocol.

5.11.4.3. ATP cohort for safety

The ATP cohort for safety included all vaccinated subjects:

- who received at least one dose of HRV vaccine or placebo,
- for whom the randomisation code was not broken,
- who did not receive a vaccine forbidden by or not specified in the protocol.

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

The total vaccinated cohort was used for the analysis of safety.

5.11.5. Derived and transformed data

Demography

For a given subject and a given demographic variable, missing measurements were 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.

Safety

In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan was re-assessed to ensure more accurate reporting of study data by further analysis.

5.11.6. Analysis of demographics

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall. The median, mean, range and standard deviation of age in months at Visit 4 and Visit 5 or at last contact if the study visit was not performed was also calculated per group and overall. The racial and gender composition per group was presented.

5.11.7. Analysis of efficacy

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

Vaccine efficacy was calculated, with their 95% confidence interval (CI) against:

- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to G1 type caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to non-G1 types during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

The primary objective was reached if the lower limit of the 95% CI on vaccine efficacy (conditional method) for the HRV group against any RV GE requiring medical intervention caused wild-type RV strains during the efficacy follow-up period was > 0%.

Vaccine efficacy was derived from a Cox regression model on the time to first event with censoring at Visit 5 for subjects without an event. The model includes the group as fixed effect [Kalbfleisch, 2002].

Incidence rate in a group (P) is computed as the number of subjects reporting at least one event (n)/total follow-up time to a first event censored at Visit 5 (T). The associated 95% CI's was obtained considering that n follows a Poisson distribution with P*T parameter.

The number of events prevented by 100 vaccinated infant-years will be obtained from 100 times the difference in the incidence rate. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008].

Additional supportive and exploratory analyses were performed (i.e. efficacy against GE of any aetiology leading to a medical intervention). An exploratory analysis was performed for vaccine efficacy against any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains by Cox method.

Similar analyses were performed for the efficacy period starting from 2 weeks post Dose 2 up to Visit 4 and from Visit 4 to Visit 5.

5.11.8. Analysis of safety

The percentage of subjects with unsolicited AEs occurring within 31-day (Day 0 – Day 30) follow-up period after any doses with its exact 95% CI was tabulated by group, by System Organ Class (SOC) and Preferred term (PT). Similar tabulation was done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and for AEs leading to drop out.

Serious adverse events reported during the study period were described in detail. The percentage of subjects with SAEs reported during the study period was tabulated by group according to MedDRA by SOC and PT, with its exact 95% CI.

The verbatim reports of unsolicited adverse events were reviewed by a physician and the signs and symptoms were coded according to MedDRA. The percentage of subjects with adverse events (serious and non-serious) leading to the withdrawal from the study with its exact 95% CI was tabulated by group SOC and PT.

5.11.9. Interim analysis

There was no interim analysis planned for this study.

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

5.12.1. Protocol amendments

Refer to Study report 107625 (Rota-056) for details on the amendment to the study protocol.

5.12.2. Other changes

The following change was made from the protocol:

- An exploratory analysis was performed for vaccine efficacy against severe RV GE leading to medical intervention by Cox method.

The following change was made from the RAP:

- The characteristics of any RV GE episodes leading to medical intervention were computed for the efficacy follow-up period on ATP cohort for efficacy.

All other analyses were performed as planned in the protocol and RAP.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject came for the first study visit on 19 June 2007 and the last visit for Visit 5 took place on 21 November 2009.

6.2. Subject eligibility and attrition from the study

6.2.1. Number of subjects

A total of 765 subjects were enrolled and received at least one dose of the HRV vaccine or placebo.

6.2.2. Study completion and withdrawal from study

Table 4 presents the number of subjects vaccinated, completed and withdrawn from the study with reasons for withdrawal.

Supplement 1 presents the number of subjects vaccinated, completed and withdrawn from the study at Visit 4 with reasons for withdrawal.

Of the 765 subjects who received at least one dose of HRV vaccine or placebo, a total of 717 subjects (476 subjects in the HRV group and 241 subjects in the placebo group) completed Visit 5. A total of 48 subjects (32 subjects in the HRV group and 16 subjects in the placebo group) were withdrawn from the study. Reasons for withdrawals were as follows:

- The parent/guardian of one subject in the HRV group withdrew their child from the study due to a serious adverse event (Hepatobiliary disorder). This medical condition developed 20 days after receiving Dose 2 and the randomization code was broken. This subject was withdrawn from the study after Visit 2. Refer to Section 8.4 for details.

- The parent/guardian of one subject in the placebo group withdrew their child from the study due to a non-serious AE (Anaphylaxis). This subject experienced the AE 38 days after receiving Dose 2 of placebo. The AE lasted only for a day and the subject was withdrawn from the study after Visit 3. Refer to Section 8.4 for details.
- One subject in the placebo group was withdrawn from the study by the investigator due to a protocol violation. This subject received a dose of Bacille Calmette-Guérin (BCG) vaccine 15 days after receiving Dose 1 of placebo.
- The parents/guardians of 19 subjects (14 subjects in the HRV group and 5 subjects in the placebo group) withdrew consent for their children to participate in the study. Consent withdrawal for these subjects was not due to an AE.
- A total of 20 subjects (15 subjects in the HRV group and 5 subjects in the placebo group) migrated from the study area and hence were unable to complete the study.
- A total of 5 subjects (2 subjects in the HRV group and 3 subjects in the placebo group) with complete vaccination course were lost to follow-up.
- One subject in the placebo group was withdrawn from the study because the subject's mother was pregnant. The decision to withdraw the child was taken by the investigator and the parents.

Table 4 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Visit 5 (Total vaccinated cohort)

	HRV	Placebo	Total
Number of subjects vaccinated	508	257	765
Number of subjects completed	476	241	717
Number of subjects withdrawn	32	16	48
Reasons for withdrawal :			
Serious Adverse Event	1	0	1
Non-serious adverse event	0	1	1
Protocol violation	0	1	1
Consent withdrawal (not due to an adverse event)	14	5	19
Migrated/moved from study area	15	5	20
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	2	3	5
Others	0	1	1

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit

6.2.3. Protocol deviations

The number of subjects enrolled and included in the ATP cohort for efficacy along with reasons for subjects excluded from the ATP cohort for efficacy is summarised in Table 5.

Total vaccinated cohort

A total of 765 subjects were enrolled into the study. All subjects (508 subjects in the HRV group and 257 subjects in the placebo group) were part of the total vaccinated cohort with at least one dose of the HRV vaccine or placebo administered.

ATP cohort for efficacy

Of the 765 subjects included in the total vaccinated cohort, 17 subjects were eliminated from the ATP cohort for efficacy for the periods starting from 2 weeks post Dose 2 up to Visit 4 and from 2 weeks post Dose 2 up to Visit 5 for the following reasons:

- The randomization code was broken for one subject in the HRV group (elimination code 1060). Refer to Section 8.4 for details.
- A total of 16 subjects (9 subjects in the HRV group and 7 subjects in the placebo group) were eliminated with code 3010 because of incomplete vaccination schedule.

Thus, a total of 748 subjects (498 subjects in the HRV group and 250 subjects in the placebo group) were included in the ATP cohort for efficacy for the periods starting from 2 weeks post Dose 2 up to Visit 4 and from 2 weeks post Dose 2 up to Visit 5.

- A total of 18 subjects (11 subjects in the HRV group and 7 subjects in the placebo group) were eliminated with code 4020 as these subjects had not entered into the surveillance period from Visit 4 to Visit 5.

Thus, a total of 730 subjects (487 subjects in the HRV group and 243 subjects in the placebo group) were included in the ATP cohort for efficacy for the period starting from Visit 4 to Visit 5.

Table 5 Number of subjects enrolled into the study as well as the number excluded from ATP analyses for efficacy with reasons for exclusion

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	765						
Total vaccinated cohort	765		100	508		257	
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0
At least one study vaccine dose not administered. (code 3010)	16	16		9	9	7	7
According-To-Protocol (ATP) cohort for Efficacy – efficacy period from 2 weeks post Dose 2 up to Visit 4/ efficacy period from 2 weeks post Dose 2 up to Visit 5	748		97.8	498		250	
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0
At least one study vaccine dose not administered. (code 3010)	16	16		9	9	7	7
Subjects not entered into the second efficacy surveillance period (code 4020)	18	27		11	17	7	10
ATP cohort for efficacy – efficacy period from Visit 4 up to Visit 5	730		95.4	487		243	

Note: Subjects may 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 vaccinated cohort

Table 6 presents the number of subjects enrolled and included in the ATP safety analyses along with the reasons for exclusion.

ATP cohort for safety

Of the 765 subjects included in the total vaccinated cohort, 1 subject in the HRV group was eliminated from the ATP cohort for safety because the randomization code was broken (elimination code 1060). Refer to 8.4 for details.

Thus, a total of 764 subjects (507 subjects in the HRV group and 257 subjects in the placebo group) were included in the ATP cohort for safety.

Table 6 Number of subjects enrolled into the study as well as the number excluded from ATP analyses for safety with reasons for exclusion

	Total			HRV		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	765						
Total vaccinated cohort	765		100	508		257	
Randomisation code broken at the investigator site (code 1060)	1	1		1	1	0	0
ATP cohort for safety	764		99.9	507		257	

Note: Subjects may 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 vaccinated cohort

Refer to Study report 107625 (Rota-056) for details 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.

Refer to Study report 107625 (Rota-056) for details on the number of subjects with deviations from specifications for age mentioned in the study inclusion criteria and intervals between study visits.

6.3. Demographic characteristics

6.3.1. ATP cohort for efficacy

Table 7 presents the summary of demographic characteristics for the ATP cohort for efficacy.

Supplement 2 presents the summary of demography characteristics for the ATP cohort for efficacy from Visit 4 to Visit 5.

- The mean age was 7.7 weeks (range: 6 to 14 weeks) at Dose 1 of HRV vaccine/placebo, 12.7 weeks (range: 10 to 20 weeks) at Dose 2 of HRV vaccine/placebo, 11.4 months (range: 4 to 13 months) at Visit 4 or at last contact if

Visit 4 was not performed and 23 months (range: 4 to 25 months) at Visit 5 or at last contact if Visit 5 was not performed.

- All the subjects were of Japanese origin; 47.6% of subjects were female and 52.4% of subjects were male.

Table 7 Summary of demographic characteristics (ATP cohort for efficacy)

		HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at dose 1 of HRV/Placebo	Mean	7.7	-	7.7	-	7.7	-
	SD	1.96	-	2.06	-	2.00	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	6	-	6	-
	Maximum	14	-	14	-	14	-
Age (weeks) at dose 2 of HRV/Placebo	Mean	12.7	-	12.7	-	12.7	-
	SD	2.03	-	2.18	-	2.08	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	19	-	20	-	20	-
Age (months) at visit 4/ Last contact if visit 4 is not performed	Mean	11.5	-	11.4	-	11.4	-
	SD	0.73	-	0.92	-	0.80	-
	Median	12.0	-	11.0	-	11.0	-
	Minimum	4	-	4	-	4	-
	Maximum	13	-	13	-	13	-
Age (months) at visit 5/ Last contact if visit 5 is not performed	Mean	23.1	-	22.9	-	23.0	-
	SD	2.36	-	2.80	-	2.51	-
	Median	23.0	-	23.0	-	23.0	-
	Minimum	4	-	4	-	4	-
	Maximum	25	-	25	-	25	-
Gender	Female	225	45.2	131	52.4	356	47.6
	Male	273	54.8	119	47.6	392	52.4
Race	Asian - Japanese heritage	498	100	250	100	748	100

N = total number of subjects in each group
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

6.3.2. Total vaccinated cohort

Supplement 3 presents the summary of demographic characteristics for the total vaccinated cohort.

- The mean age was 7.7 weeks (range: 5 to 14 weeks) at Dose 1 of HRV/placebo, 12.7 weeks (range: 10 to 20 weeks) at Dose 2 of HRV/placebo, 11.4 months (range: 1 to 13 months) at Visit 4 or last contact if Visit 4 was not performed and 22.8 months (range: 1 to 25 months) at Visit 5 or last contact if Visit 5 was not performed.
- One subject was unblinded before the data lock point (01 March 2010) (Supplement 4). Refer to Section 8.4 for details.

6.3.3. Concomitant and Intercurrent Vaccinations

Routine childhood vaccinations according to local practice could be administered concurrently with the study vaccinations as recommended in Japan.

Unblinded results of the vaccinations administered other than the HRV vaccine/placebo during the study period is presented in this section.

- Only one subject (0.4%) in the placebo group received a single dose of Hepatitis B virus (HBV) vaccine before Dose 1; one subject (0.4%) in the placebo group received a single dose of HBV vaccine between Dose 1 and Dose 2 and one subject (0.2%) in the HRV group received a single dose of HBV vaccine between Dose 2 and Visit 3.

Refer to Study report 107625 (Rota-056) for details on the concomitant and intercurrent vaccinations.

7. VACCINE EFFICACY RESULTS

7.1. Data sets analysed

Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) for vaccine efficacy during the period starting from 2 weeks post Dose 2 up to Visit 4, for the vaccine efficacy during the period starting from 2 weeks post Dose 2 up to Visit 5, for the vaccine efficacy during the period starting from Visit 4 up to Visit 5 and on the total vaccinated cohort for the vaccine efficacy from Dose 1 up to Visit 5. See Section 5.11.4 for the definition of the cohorts identified for analyses and Section 6.2.3 for eligibility for analyses.

Vaccine virus was not isolated from any of the GE stool samples collected in the study from Dose 1 up to Visit 5.

7.2. Vaccine efficacy during the efficacy period starting from 2 weeks post Dose 2 up to Visit 5

The ATP cohort for efficacy during the period starting from 2 weeks post Dose 2 up to Visit 5 included 748 subjects (498 subjects in the HRV group and 250 subjects in the placebo group).

7.2.1. Characteristics of GE episodes leading to medical intervention

Table 8 presents the percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to Visit 5.

- A total of 201 subjects (40.4%) from the HRV group and 111 subjects (44.4%) from the placebo group had a report of at least one GE episode leading to medical intervention.

- There were 2 subjects (0.4%) from the HRV group and 12 subjects (4.8%) from the placebo group with report of severe RV GE episodes leading to medical intervention.
- When the GE and RV GE episodes leading to medical intervention were scored using the 20-point Vesikari scale, the distribution of reported GE episodes leading to medical intervention among mild, moderate and severe intensity was similar in both groups.
- When the RV GE episodes leading to medical intervention were scored using the 20-point Vesikari scale, there were more cases rated as severe (≥11 points) in the placebo group (12 RV GE episodes [35.3%] as compared to the HRV group (2 RV GE episodes [14.3%]).

Supplement 5 presents the percentage of GE episodes leading to medical intervention with no available stool results from 2 weeks post Dose 2 up to Visit 5.

Stool analysis results were not available for 23 (7.3%) GE episodes in the HRV group and for 6 (3.5%) GE episodes in the placebo group because stool samples were either not tested or not collected.

Table 8 Percentage of subjects who reported GE episodes, RV GE episodes, Severe RV GE episodes, and severe GE episodes leading to medical intervention from 2 weeks post Dose 2 to up to Visit 5 (ATP cohort for efficacy)

		HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	**Number of episodes**	**n**	**%**	**n**	**%**	**n**	**%**
GE	1	131	26.3	72	28.8	203	27.1
	2	47	9.4	24	9.6	71	9.5
	3	12	2.4	13	5.2	25	3.3
	4	7	1.4	1	0.4	8	1.1
	5	2	0.4	0	0.0	2	0.3
	7	2	0.4	1	0.4	3	0.4
	Any	201	40.4	111	44.4	312	41.7
RV GE	1	14	2.8	34	13.6	48	6.4
	Any	14	2.8	34	13.6	48	6.4
Severe GE	1	32	6.4	22	8.8	54	7.2
	2	3	0.6	4	1.6	7	0.9
	Any	35	7.0	26	10.4	61	8.2
Severe RV GE	1	2	0.4	12	4.8	14	1.9
	Any	2	0.4	12	4.8	14	1.9

HRV = HRV group
Placebo = Placebo group
N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified number of episode
Any = number (percentage) of subjects reporting at least one specified symptom

Table 9 Number of GE episode and RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

		HRV		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%
GE	Mild (1-6)	164	52.4	82	48.2
	Moderate (7-10)	111	35.5	58	34.1
	Severe (≥11)	38	12.1	30	17.6
	Any	313	100	170	100
RV GE	Mild (1-6)	6	42.9	10	29.4
	Moderate (7-10)	6	42.9	12	35.3
	Severe (≥11)	2	14.3	12	35.3
	Any	14	100	34	100

HRV = HRV group
Placebo = Placebo group
n (%) = Number (percentage) of specified events reported in each group, by severity using the 20 point Vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy follow-up period

Supplement 6 and Supplement 7 present the percentage of any and severe RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5, by G and P type, respectively.

Table 10 presents the number of severe RV GE episodes leading to medical intervention by G and P type.

Among the severe RV GE episodes leading to medical intervention, G1P[8] (1 episode in the HRV group and 6 episodes in the placebo group) followed by G9P[8] (1 episode in the HRV group and 2 episodes in the placebo group) and G3P[8] (none in the HRV group and 4 episodes in the placebo group) were the predominant RV types circulating during the period starting from 2 weeks post Dose 2 up to Visit 5.

Table 10 Number of severe RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5, by G and P type (ATP cohort for efficacy)

Type	HRV		Placebo	
	n	%	n	%
Any	2	100.0	12	100.0
G1WT+P8WT	1	50.00	6	50.00
G3+P8WT	0	0.00	4	33.33
G9+P8WT	1	50.00	2	16.67

HRV = HRV group
Placebo = Placebo group
n (%) = number (percentage) of severe RV GE episodes reporting the specified RV type in each group, among all severe RV GE episodes reported from 2 weeks post dose 2 up to visit 5
Any = any specified symptom reported, regardless of the RV type

Supplement 8 presents the number of subjects with RV GE episodes leading to medical intervention by G and P type.

Among the RV GE episodes leading to medical intervention, G1P[8] (4 episodes in the HRV group and 13 episodes in the placebo group) and G3P[8] (3 episodes in the HRV group and 13 episodes in the placebo group) were the predominant RV types circulating during the period from 2 weeks post Dose 2 up to Visit 5. The other RV types isolated were G2P[4] (1 episode in the HRV group and 2 episodes in the placebo group), G4P[8] (1 episode each in both groups) and G9P[8] (5 episodes each in both groups).

Supplement 9 presents the characteristics of RV GE episodes leading to medical intervention based on the Vesikari scale reported from 2 weeks post Dose 2 up to Visit 5.

Supplement 10 to Supplement 14 present the characteristics of RV GE episodes leading to medical intervention based on the Vesikari scale by G types reported from 2 weeks post Dose 2 up to Visit 5.

Supplement 15 presents the distribution of the Vesikari score for RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5.

The incidence of RV GE leading to medical intervention rated 5 and below on the Vesikari scale was similar in both groups but the incidence of RV GE leading to medical intervention rated more than 5 on the Vesikari scale was much higher in the placebo group as compared to the HRV group.

Supplement 16 presents the duration (in years) of efficacy follow-up from 2 weeks post Dose 2 up to Visit 5.

The mean duration of the combined efficacy follow-up period from 2 weeks post Dose 2 up to Visit 5 was 1.68 years in the HRV group and 1.67 years in the placebo group.

7.2.2. Vaccine efficacy against any RV GE leading to medical intervention

Table 11 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild-type RV leading to medical intervention from 2 weeks post Dose 2 up to Visit 5.

- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (2.8% versus 13.6%; p-value <0.001) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against any RV GE episodes leading to medical intervention caused by the circulating wild-type RV was 79.3% [95% CI: 60.5%; 89.8%]. The primary objective of the study was reached since the lower limit of the 95% CI on vaccine efficacy was >0% (criteria specified for fulfilling the primary efficacy objective).

Table 11 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	14	2.8	1.5	4.7	79.3	60.5	89.8	<0.001
Placebo	250	34	13.6	9.6	18.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Using the Cox proportional-hazard model, vaccine efficacy against any RV GE episode leading to medical intervention caused by the circulating wild-type RV was 80.65% [95% CI: 63.95%; 89.62%]. A total of 7 any RV GE episodes leading to medical intervention per 100 infant years could be prevented by vaccination (Supplement 17 and Supplement 18).

7.2.3. Vaccine efficacy against severe RV GE leading to medical intervention

Table 12 presents the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV from 2 weeks post Dose 2 up to Visit 5.

- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (0.4% versus 4.8%; p-value <0.001) from 2 weeks post Dose 2 up to Visit 5. Vaccine efficacy against severe RV GE leading to medical intervention caused by circulating wild-type RV was 91.6% [95% CI: 62.4%; 99.1%].

Table 12 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	2	0.4	0.0	1.4	91.6	62.4	99.1	<0.001
Placebo	250	12	4.8	2.5	8.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Using the Cox proportional-hazard model, vaccine efficacy against severe RV GE episode leading to medical intervention caused by the circulating wild-type RV was 91.86% [95% CI: 63.65%; 98.18%]. A total of 2.7 severe RV GE episodes leading to medical intervention per 100 infant years could be prevented by vaccination (Supplement 19 and Supplement 18).

Supplement 20 and Supplement 21 present the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention with a score ≥ a specific value (≥11 – ≥20) on the Vesikari scale.

7.2.4. Vaccine efficacy against circulating RV types

7.2.4.1. Vaccine efficacy against any RV GE leading to medical intervention by RV type

Table 13 presents the efficacy of the HRV vaccine against any RV GE episodes leading to medical intervention, by isolated RV types from 2 weeks post Dose 2 up to Visit 5.

- The percentage of subjects with report of any RV GE leading to medical intervention caused by G1 wild type in the HRV group was significantly lower compared to the placebo group (0.8% versus 5.2%; p-value <0.001). Vaccine efficacy against any RV GE episodes caused by G1 wild type leading to medical intervention was 84.6% [95% CI: 50.0%; 96.3%].
- When considering all isolated non-G1 types (G2, G3, G4 and G9), significantly fewer subjects in the HRV group reported any RV GE leading to medical intervention compared to the placebo group (2.0% versus 8.4%; p-value <0.001). Vaccine efficacy against any RV GE caused by non-G1 types leading to medical intervention was 76.1% [95% CI: 47.0%; 89.9%].
- Any RV GE episodes leading to medical intervention caused by G2 type and P[4] type were reported for 0.2% of the subjects in the HRV group and for 0.8% of the subjects in the placebo group (p-value 0.521). Vaccine efficacy against any RV GE episodes leading to medical intervention caused by G2 type and P[4] type was 74.9% [95% CI: -382.2%; 99.6%].
- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by G3 type compared to the placebo group (0.6% versus 5.2%; p-value <0.001). Vaccine efficacy against any RV GE episodes leading to medical intervention caused by G3 type was 88.4% [95% CI: 57.8%; 97.9%].
- Any RV GE episodes leading to medical intervention caused by G4 type were reported for 0.2% of subjects in the HRV group and 0.4% of subjects in the placebo group (p-value 1.000). Vaccine efficacy against any RV GE leading to medical intervention caused by G4 type was 49.8% [95% CI: -3840.6%; 99.4%].
- Any RV GE episodes leading to medical intervention caused by G9 type were reported for 1.0% of subjects in the HRV group and for 2.0% of subjects in the placebo group (p-value 0.430). Vaccine efficacy against any RV GE leading to medical intervention caused by G9 type was 49.8% [95% CI: -118.1%; 88.4%].

- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by P[8] type compared to the placebo group (2.6% versus 12.8%; p-value <0.001). Vaccine efficacy against any RV GE leading to medical intervention caused by P[8] type was 79.6% [95% CI: 60.1%; 90.2%].

Table 13 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 5 – by type (ATP cohort for efficacy)

				n/N			VE			
Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV	498	4	0.8	0.2	2.0	84.6	50.0	96.3	<0.001
	Placebo	250	13	5.2	2.8	8.7	-	-	-	-
G2	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
G3	HRV	498	3	0.6	0.1	1.8	88.4	57.8	97.9	<0.001
	Placebo	250	13	5.2	2.8	8.7	-	-	-	-
G4	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
G9	HRV	498	5	1.0	0.3	2.3	49.8	-118.1	88.4	0.430
	Placebo	250	5	2.0	0.7	4.6	-	-	-	-
P8WT	HRV	498	13	2.6	1.4	4.4	79.6	60.1	90.2	<0.001
	Placebo	250	32	12.8	8.9	17.6	-	-	-	-
P4	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
Pooled	HRV	498	10	2.0	1.0	3.7	76.1	47.0	89.9	<0.001
Non-G1	Placebo	250	21	8.4	5.3	12.6	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

7.2.4.2. Vaccine efficacy against severe RV GE leading to medical intervention by RV type

Table 14 presents the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention by isolated RV types from 2 weeks post Dose 2 up to Visit 5.

- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by G1 wild-type compared to the placebo group (0.2% versus 2.4%; p-value 0.014). Vaccine efficacy against severe RV GE caused by G1 wild-type RV leading to medical intervention was 91.6% [95% CI: 31.0%; 99.8%].
- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by non-G1 types compared to the placebo (0.2% versus 2.4%; p-value 0.014). Vaccine efficacy against severe RV GE leading to medical intervention caused by non-G1 type was 91.6% [95% CI: 31.0%; 99.8%].

- Severe RV GE caused by G3 type leading to medical intervention was reported for 1.6% of the subjects in the placebo group. There were no reports of severe RV GE caused by G3 type leading to medical intervention in the HRV group. Vaccine efficacy against severe RV GE leading to medical intervention caused by G3 type was 100.0% [95% CI: 24.0%; 100.0%].
- Severe RV GE episodes leading to medical intervention caused by G9 type were reported for 0.2% of subjects in the HRV group and for 0.8% of subjects in the placebo group (p-value 0.521). Vaccine efficacy against severe RV GE episodes leading to medical intervention caused by G9 type was 74.9% [95% CI: -382.2%; 99.6%].
- Significantly fewer subjects in the HRV group reported severe RV GE episodes caused by P[8] type compared to the placebo group (0.4% versus 4.8%; p-value <0.001). Vaccine efficacy against severe RV GE leading to medical intervention caused by P[8] type was 91.6% [95% CI: 62.4%; 99.1%].

Table 14 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks after dose 2 up to visit 5 – by type (ATP cohort for efficacy)

				n/N			VE			
Type	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
G1WT	HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
	Placebo	250	6	2.4	0.9	5.2	-	-	-	-
G3	HRV	498	0	0.0	0.0	0.7	100.0	24.0	100.0	0.025
	Placebo	250	4	1.6	0.4	4.0	-	-	-	-
G9	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
P8WT	HRV	498	2	0.4	0.0	1.4	91.6	62.4	99.1	<0.001
	Placebo	250	12	4.8	2.5	8.2	-	-	-	-
Pooled	HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
Non-G1	Placebo	250	6	2.4	0.9	5.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

7.2.5. Vaccine efficacy against hospitalisation due to RV GE

Table 15 presents the efficacy of the HRV vaccine against hospitalisation due to RV GE leading to medical intervention from 2 weeks post Dose 2 up to Visit 5.

- There were very few reports of hospitalisation due to RV GE leading to medical intervention (1 subject in the HRV group and 2 subjects in the placebo group).

Table 15 Percentage of subjects hospitalised due to RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 5 - (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
Placebo	250	2	0.8	0.1	2.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

7.2.6. Vaccine efficacy against all cause GE

Supplement 22 presents the efficacy of the HRV vaccine against all cause GE episodes leading to medical intervention from 2 weeks post Dose 2 up to Visit 5.

- All cause GE episodes leading to medical intervention was reported for 40.4% of subjects in the HRV group and for 44.4% of subjects in the placebo group (p-value 0.453). Vaccine efficacy against all cause GE episodes leading to medical intervention was 9.1% [95% CI: -15.7%; 28.3%].

Supplement 23 presents the efficacy of the HRV vaccine against all cause severe GE episodes leading to medical intervention from 2 weeks post Dose 2 up to Visit 5.

Supplement 24 presents the efficacy of the HRV vaccine against hospitalisation due to GE episodes leading to medical intervention from 2 weeks post Dose 2 up to Visit 5.

7.3. ATP cohort for efficacy during the period starting from 2 weeks post Dose 2 up to Visit 4

The ATP cohort for efficacy for the period starting from 2 weeks post Dose 2 up to Visit 4 included 748 subjects (498 subjects in the HRV group and 250 subjects in the placebo group).

7.3.1. Characterisation of GE episodes leading to medical intervention

Table 16 presents the percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to Visit 4. Table 17 presents the summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 4.

- A total of 119 subjects (23.9%) from the HRV group and 74 subjects (29.6%) from the placebo group had report of at least one GE episode leading to medical intervention.

- There was 1 (0.2%) subject with severe RV GE episode in the HRV group and 4 (1.6%) subjects with severe RV GE episodes in the placebo group.
- When the GE and RV GE episodes leading to medical intervention were scored using the 20-point Vesikari scale, the distribution of reported GE episodes leading to medical intervention among mild, moderate and severe intensity was similar in both groups.
- When the RV GE episodes leading to medical intervention were scored using the 20-point Vesikari scale, there were more cases rated as severe (≥11 points) in the placebo group (4 RV GE episodes [33.3%]) as compared to the HRV group (1 RV GE episode [20.0%]).

Supplement 25 presents the percentage of GE episodes leading to medical intervention with no available stool results from 2 weeks post Dose 2 up to Visit 4.

Stool analysis results were not available for 13 (8.4%) GE episodes in the HRV group and for 4 (4.3%) GE episodes in the placebo group because stool samples were either not tested or not collected.

Table 16 Percentage of subjects who reported GE episodes, RV GE episodes, Severe RV GE episodes, and severe GE episodes leading to medical intervention from 2 weeks post dose 2 to up to visit 4 (ATP cohort for efficacy)

		HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	**Number of episodes**	**n**	**%**	**n**	**%**	**n**	**%**
GE	1	93	18.7	59	23.6	152	20.3
	2	18	3.6	12	4.8	30	4.0
	3	6	1.2	3	1.2	9	1.2
	4	2	0.4	0	0.0	2	0.3
	Any	119	23.9	74	29.6	193	25.8
RV GE	1	5	1.0	12	4.8	17	2.3
	Any	5	1.0	12	4.8	17	2.3
Severe GE	1	13	2.6	9	3.6	22	2.9
	2	1	0.2	1	0.4	2	0.3
	Any	14	2.8	10	4.0	24	3.2
Severe RV GE	1	1	0.2	4	1.6	5	0.7
	Any	1	0.2	4	1.6	5	0.7

HRV = HRV group
Placebo = Placebo group
N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified number of episode
Any = number (percentage) of subjects reporting at least one specified symptom

Table 17 Number of GE episode and RV GE episodes leading to medical intervention reported from 2 weeks post dose 2 up to visit 4 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

		HRV		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%
GE	Mild (1-6)	78	50.3	43	46.7
	Moderate (7-10)	62	40.0	38	41.3
	Severe (≥11)	15	9.7	11	12.0
	Any	155	100	92	100
RV GE	Mild (1-6)	3	60.0	4	33.3
	Moderate (7-10)	1	20.0	4	33.3
	Severe (≥11)	1	20.0	4	33.3
	Any	5	100	12	100

HRV = HRV group
Placebo = Placebo group
n (%) = Number (percentage) of specified events reported in each group, by severity using the 20 point Vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy follow-up period

Supplement 26 and Supplement 27 present the percentage of any and severe RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 4, by G and P type, respectively.

Table 18 presents the number of subjects with severe RV GE episodes leading to medical intervention by G and P type.

Among the severe RV GE episodes leading to medical intervention, G9P[8] (1 episode in the HRV group and 2 episodes in the placebo group) followed by G3P[8] (none in the HRV group and 2 episodes in the placebo group) were the predominant RV types circulating during the period starting from 2 weeks post Dose 2 up to Visit 4.

Table 18 Number of severe RV GE episodes leading to medical intervention reported from 2 weeks post dose 2 up to visit 4, by G and P type (ATP cohort for efficacy)

Type	HRV		Placebo	
	n	%	n	%
Any	1	100.0	4	100.0
G3+P8WT	0	0.00	2	50.00
G9+P8WT	1	100.0	2	50.00

HRV = HRV group
Placebo = Placebo group
n (%) = number (percentage) of severe RV GE episodes reporting the specified RV type in each group, among all severe RV GE episodes reported from 2 weeks post dose 2 up to visit 4
Any = any specified symptom reported, regardless of the RV type

Supplement 28 presents the number of subjects with RV GE episodes leading to medical intervention by G and P type.

Among the RV GE episodes leading to medical intervention, G3P[8] (1 episode in the HRV group and 6 episodes in the placebo group) and G9P[8] (3 episodes in the HRV group and 4 episodes in the placebo group) were the most predominant RV types circulating during the period starting from 2 weeks post Dose 2 up to Visit 4. The other RV type isolated was G4P[8] (1 episode each in both groups).

Supplement 29 presents the characteristics of RV GE episodes leading to medical intervention based on the Vesikari scale reported from 2 weeks post Dose 2 up to Visit 4.

Supplement 30 to Supplement 33 present the characteristics of RV GE episodes leading to medical intervention based on the Vesikari scale by G types reported from 2 weeks post Dose 2 up to Visit 4.

Supplement 34 presents the distribution of the Vesikari score for RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 4.

The incidence of RV GE leading to medical intervention rated 6 and below on the Vesikari scale was similar in both groups but the incidence of RV GE leading to medical intervention rated more than 6 on the Vesikari scale was much higher in the placebo group as compared to the HRV group.

Supplement 35 presents the duration (in years) of efficacy follow-up from 2 weeks post Dose 2 up to Visit 4.

The mean duration of the first efficacy follow-up period from 2 weeks post Dose 2 up to Visit 4 was 0.71 years in the HRV group and 0.70 years in the placebo group.

7.3.2. Vaccine efficacy against any RV GE leading to medical intervention

Table 19 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild-type RV leading to medical intervention from 2 weeks post Dose 2 up to Visit 4.

- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (1.0% versus 4.8%; p-value 0.004) from 2 weeks post Dose 2 up to Visit 4. Vaccine efficacy against any RV GE episodes leading to medical intervention caused by the circulating wild-type RV was 79.1% [95% CI: 36.2%; 94.2%].

Table 19 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 4 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	5	1.0	0.3	2.3	79.1	36.2	94.2	0.004
Placebo	250	12	4.8	2.5	8.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Using the Cox proportional-hazard model, vaccine efficacy against any RV GE episodes leading to medical intervention caused by the circulating wild-type RV was 79.83% [95% CI: 42.75%; 92.89%]. A total of 5.6 any RV GE episodes leading to medical intervention per 100 infant years could be prevented by vaccination (Supplement 36 and Supplement 37).

7.3.3. Vaccine efficacy against severe RV GE leading to medical intervention

Table 20 presents the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV from 2 weeks post Dose 2 up to Visit 4.

- The percentage of subjects with report of severe RV GE episodes leading to medical intervention caused by circulating wild-type RV was lower in the HRV group compared to the placebo group (0.2% versus 1.6%; p-value 0.091). Vaccine efficacy against severe RV GE episodes leading to medical intervention caused by circulating wild-type RV was 87.4% [95% CI: -26.8%; 99.7%].

Table 20 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 4 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	1	0.2	0.0	1.1	87.4	-26.8	99.7	0.091
Placebo	250	4	1.6	0.4	4.0	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Using the Cox proportional-hazard model, vaccine efficacy against severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV was

87.68% [95% CI: -10.14%; 98.62%]. A total of 2 severe RV GE episodes leading to medical intervention per 100 infant years could be prevented by vaccination (Supplement 38 and Supplement 37).

Supplement 39 and Supplement 40 present the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention with a score ≥ a specific value (≥11 – ≥20) on the Vesikari scale.

7.3.4. Vaccine efficacy against circulating RV types

7.3.4.1. Vaccine efficacy against any RV GE leading to medical intervention by RV type

Table 21 presents the efficacy of the HRV vaccine against any RV GE episodes leading to medical intervention, by isolated RV types from 2 weeks post Dose 2 up to Visit 4.

- Any RV GE episodes leading to medical intervention caused by non-G1 types were reported for 1.0% of subjects in the HRV group and for 4.8% of subjects in the placebo group (p-value 0.004). Vaccine efficacy against any RV GE caused by non-G1 types leading to medical intervention was 79.1% [95% CI: 36.2%; 94.2%].
- Any RV GE episodes leading to medical intervention caused by G2 type were reported for none in the HRV group and for 0.4% of subjects in the placebo group (p-value 0.668). Vaccine efficacy against any RV GE leading to medical intervention caused by G2 type was 100.0% [95% CI: -1857.8%; 100.0%].
- Any RV GE episodes leading to medical intervention caused by G3 type were reported for 0.2% of subjects in the HRV group and 2.4% of subjects in the placebo group (p-value 0.014). Vaccine efficacy against any RV GE leading to medical intervention caused by G3 type was 91.6% [95% CI: 31.0%; 99.8%].
- Any RV GE episodes leading to medical intervention caused by G4 type were reported for 0.2% of subjects in the HRV group and 0.4% of subjects in the placebo group (p-value 1.000). Vaccine efficacy against any RV GE leading to medical intervention caused by G4 type was 49.8% [95% CI: -3840%; 99.4%].
- Any RV GE episodes leading to medical intervention caused by G9 type were reported for 0.6% of subjects in the HRV group and 1.6% of subjects in the placebo group (p-value 0.349). Vaccine efficacy against any RV GE leading to medical intervention caused by G9 type was 62.3% [95% CI: -122.6%; 94.5%].
- Any RV GE episodes leading to medical intervention caused by P[8] type were reported for 1.0% of subjects in the HRV group and 4.4% of subjects in the placebo group (p-value 0.008). Vaccine efficacy against any RV GE leading to medical intervention caused by P[8] type was 77.2% [95% CI: 28.8%; 93.8%].
- Any RV GE episodes leading to medical intervention caused by P[4] type were reported for 0.4% of subjects in the placebo group (p-value 0.668). Vaccine efficacy against any RV GE leading to medical intervention caused by P[4] type was 100.0% [95% CI: -1857.8%; 100.0%].

Table 21 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 4 – by type (ATP cohort for efficacy)

				n/N			VE			
Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G2	HRV	498	0	0.0	0.0	0.7	100.0	-1857.8	100.0	0.668
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
G3	HRV	498	1	0.2	0.0	1.1	91.6	31.0	99.8	0.014
	Placebo	250	6	2.4	0.9	5.2	-	-	-	-
G4	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
G9	HRV	498	3	0.6	0.1	1.8	62.3	-122.6	94.5	0.349
	Placebo	250	4	1.6	0.4	4.0	-	-	-	-
P8WT	HRV	498	5	1.0	0.3	2.3	77.2	28.8	93.8	0.008
	Placebo	250	11	4.4	2.2	7.7	-	-	-	-
P4	HRV	498	0	0.0	0.0	0.7	100.0	-1857.8	100.0	0.668
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
Pooled	HRV	498	5	1.0	0.3	2.3	79.1	36.2	94.2	0.004
Non-G1	Placebo	250	12	4.8	2.5	8.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

7.3.4.2. Vaccine efficacy against severe RV GE leading to medical intervention by RV type

Table 22 presents the efficacy of the HRV vaccine against severe RV GE episodes leading to medical intervention, by isolated RV types from 2 weeks post Dose 2 up to Visit 4.

- Severe RV GE episodes leading to medical intervention caused by non-G1 types were reported for 0.2% of subjects in the HRV group and for 1.6% of subjects in the placebo group (p-value 0.091). Vaccine efficacy against severe RV GE caused by non-G1 types leading to medical intervention was 87.4% [95% CI: -26.8%; 99.7%].
- Severe RV GE episodes leading to medical intervention caused by G3 type were reported for none of the subjects in the HRV group and for 0.8% of subjects in the placebo group (p-value 0.223). Vaccine efficacy against severe RV GE leading to medical intervention caused by G3 type leading to medical intervention was 100.0% [95% CI: -167.3%; 100.0%].
- Severe RV GE episodes leading to medical intervention caused by G9 type were reported for 0.2% of subjects in the HRV group and 0.8% of subjects in the placebo group (p-value 0.521). Vaccine efficacy against severe RV GE leading to medical intervention caused by G9 type leading to medical intervention was 74.9% [95% CI: -382.2%; 99.6%].

- Severe RV GE episodes leading to medical intervention caused by P[8] type were reported for 0.2% of subjects in the HRV group and 1.6% of subjects in the placebo group (p-value 0.091). Vaccine efficacy against severe RV GE leading to medical intervention caused by P[8] type leading to medical intervention was 87.4% [95% CI: -26.8%; 99.7%].

Table 22 Percentage of subjects reporting severe RV GE episode leading to medical intervention and efficacy of the vaccine from 2 weeks after dose 2 up to visit 4 – by type (ATP cohort for efficacy)

				n/N			VE			
Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G3	HRV	498	0	0.0	0.0	0.7	100.0	-167.3	100.0	0.223
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
G9	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
P8WT	HRV	498	1	0.2	0.0	1.1	87.4	-26.8	99.7	0.091
	Placebo	250	4	1.6	0.4	4.0	-	-	-	-
Any	HRV	498	1	0.2	0.0	1.1	87.4	-26.8	99.7	0.091
	Placebo	250	4	1.6	0.4	4.0	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Any = any specified symptom reported, regardless of the RV type

7.3.5. Vaccine efficacy against hospitalisation due to RV GE

Table 23 presents the efficacy of the HRV vaccine against hospitalisation due to RV GE leading to medical intervention from 2 weeks post Dose 2 up to Visit 4.

- There were few reports of hospitalisation due to RV GE leading to medical intervention (1 subject in each group).

Table 23 Percentage of subjects hospitalised due to RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post dose 2 up to visit 4 - (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
Placebo	250	1	0.4	0.0	2.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

7.3.6. Vaccine efficacy against all cause GE

Supplement 41 presents the efficacy of the HRV vaccine against all cause GE episodes leading to medical intervention from 2 weeks post Dose 2 up to Visit 4.

- All cause GE episodes leading to medical intervention was reported for 23.9% of subjects in the HRV group and for 29.6% of subjects in the placebo group (p-value 0.172). Vaccine efficacy against all cause GE episodes leading to medical intervention was 19.3% [95% CI: -9.4%; 40.1%].

Supplement 42 presents the efficacy of the HRV vaccine against all cause severe GE episodes leading to medical intervention from 2 weeks post Dose 2 up to Visit 4.

Supplement 43 presents the efficacy of the HRV vaccine against hospitalisation due to GE episodes leading to medical intervention from 2 weeks post Dose 2 up to Visit 4.

7.4. ATP cohort for efficacy during the period from Visit 4 up to Visit 5

The ATP cohort for efficacy for the efficacy follow-up period from Visit 4 up to Visit 5 included 730 subjects (487 subjects in the HRV group and 243 subjects in the placebo group).

7.4.1. Vaccine efficacy against RV GE leading to medical intervention from Visit 4 to Visit 5

Table 24 presents the efficacy of the HRV vaccine during the efficacy period from Visit 4 to Visit 5.

Supplement 44 to Supplement 67 present the results for the efficacy period from Visit 4 to Visit 5.

- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (1.8% versus 9.1%; p-value <0.001) from Visit 4 to Visit 5. Vaccine efficacy against any RV GE episodes leading to medical intervention caused by the circulating wild-type RV was 79.6% [95% CI: 53.9%; 91.7%].
- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV compared to the placebo group (0.2% versus 3.3%; p-value 0.002). Vaccine efficacy against severe RV GE episodes leading to medical intervention caused by the circulating wild-type RV was 93.8% [95% CI: 53.5%; 99.9%].
- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused G1 wild-type compared to the placebo group (0.8% versus 5.3%; p-value <0.001). Vaccine efficacy against any RV GE episodes leading to medical intervention caused by G1 wild-type was 84.6% [95% CI: 50.3%; 96.4%].

- Significantly fewer subjects in the HRV group reported severe RV GE episodes leading to medical intervention caused G1 wild-type compared to the placebo group (0.2% versus 2.5%; p-value 0.014). Vaccine efficacy against severe RV GE caused by G1 wild-type RV leading to medical intervention was 91.7% [95% CI: 31.5%; 99.8%].
- Significantly fewer subjects in the HRV group reported any RV GE episodes leading to medical intervention caused by non-G1 type leading to medical intervention compared to the placebo group (1.0% versus 3.7%; p-value 0.035). Vaccine efficacy against any RV GE leading to medical intervention caused by non-G1 type was 72.3% [95% CI: 7.9%; 92.7%].
- Severe RV GE caused by non-G1 type leading to medical intervention was reported for 0.8% of subjects in the placebo group. There were no reports of severe RV GE leading to medical intervention caused by non-G1 type in the HRV group. Vaccine efficacy against severe RV GE leading to medical intervention caused by non-G1 type was 100.0% [95% CI: -165.7%; 100.0%].
- One subject in the placebo group was hospitalised due to RV GE leading to medical intervention.

Table 24 Percentage of subjects reporting any and severe RV GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 to Visit 5 - ATP cohort for efficacy

Group	N	n	n/N			Vaccine Efficacy			P-value
				95% CI			95% CI		
			%	LL	UL	%	LL	UL	
Any RV GE due to circulating wild-type RV leading to medical intervention									
HRV	487	9	1.8	0.8	3.5	79.6	53.9	91.7	<0.001
Placebo	243	22	9.1	5.8	13.4	-	-	-	-
Severe* RV GE due to circulating wild-type RV leading to medical intervention									
HRV	487	1	0.2	0.0	1.1	93.8	53.5	99.9	0.002
Placebo	243	8	3.3	1.4	6.4	-	-	-	-
Any RV GE due to wild-type G1									
HRV	487	4	0.8	0.2	2.1	84.6	50.3	96.4	<0.001
Placebo	243	13	5.3	2.9	9.0	-	-	-	-
Severe* RV GE due to wild-type G1									
HRV	487	1	0.2	0.0	1.1	91.7	31.5	99.8	0.014
Placebo	243	6	2.5	0.9	5.3	-	-	-	-
Any RV GE due to non-G1 types									
HRV	487	5	1.0	0.3	2.4	72.3	7.9	92.7	0.035
Placebo	243	9	3.7	1.7	6.9	-	-	-	-
Severe* RV GE due to non-G1 types									
HRV	487	0	0.0	0.0	0.8	100.0	-165.7	100.0	0.222
Placebo	243	2	0.8	0.1	2.9	-	-	-	-
Hospitalization due to RV GE									
HRV	487	0	0.0	0.0	0.8	100.0	-1846.0	100.0	0.666
Placebo	243	1	0.4	0.0	2.3	-	-	-	-

HRV = HRV group
Placebo = Placebo group
*episodes with score ≥ 11 points on Vesikari scale
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

7.5. Total Vaccinated Cohort

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

Supplement 68 to Supplement 80 present results for vaccine efficacy during the period starting from Dose 1 up to Visit 5.

Efficacy estimates for the period from Dose 1 up to Visit 5 (mean duration: 1.79 years in the HRV group and 1.78 years in the placebo group) were consistent with the results of the primary analysis on the ATP cohort for efficacy for the period starting from 2 weeks post Dose 2 up to Visit 5.

- During the period starting from Dose 1 up to Visit 5, significantly fewer subjects reported any RV GE caused by wild-type RV leading to medical intervention in the HRV group compared to the placebo group (2.8% versus 14.0%; p-value <0.001).

Vaccine efficacy against any RV GE caused by wild-type RV leading to medical intervention was 80.3% [95% CI: 62.6%; 90.2%].

- During the period starting from Dose 1 up to Visit 5, significantly fewer subjects reported severe RV GE caused by wild-type RV leading to medical intervention in the HRV group compared to the placebo group (0.4% versus 5.1%; p-value <0.001). Vaccine efficacy against severe RV GE caused by wild-type RV leading to medical intervention was 92.2% [95% CI: 65.6%; 99.1%].

Supplement 81 to Supplement 91 present the results for vaccine efficacy during the period from Dose 1 up to 2 weeks post Dose 2.

7.6. Efficacy conclusions

- Two doses of the HRV vaccine were found to be highly effective against any RV GE caused by wild-type RV leading to medical intervention during the efficacy period starting from 2 weeks post Dose 2 up to Visit 5 with a vaccine efficacy of 79.3% [95% CI: 60.5%; 89.8%] thereby meeting the primary objective of the study.
- Two doses of HRV vaccine were found to be highly efficacious against:
  - Severe RV GE caused by the circulating wild-type RV leading to medical intervention with a vaccine efficacy of 91.6% [95% CI: 62.4%; 99.1%].
  - Any RV GE episodes caused by G1 wild-type RV leading to medical intervention with a vaccine efficacy of 84.6% [95% CI: 50.0%; 96.3%].
  - Severe RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
  - Any RV GE leading to medical intervention caused by non-G1 RV type with a vaccine efficacy of 76.1% [95% CI: 47.0%; 89.9%].
  - Severe RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
- There were very few reports of hospitalisation due to RV GE leading to medical intervention (1 subject in the HRV group and 2 subjects in the placebo group).
- During the period starting from Dose 1 up to Visit 5, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 80.3% [95% CI: 62.6%; 90.2%] and 92.2% [95% CI: 65.6%; 99.1%], respectively.

8. SAFETY RESULTS

8.1. Data sets analysed

The analysis of safety was performed on the Total vaccinated cohort. See Section 5.11.4 for the definition of the cohorts identified for analyses and Section 6.2 for eligibility for analyses.

8.2. Total vaccinated cohort analysis

The total vaccinated cohort included 508 subjects in the HRV group and 257 subjects in the placebo group.

8.2.1. Unsolicited adverse events

Unblinded results of unsolicited adverse events reported during the 31-day (Day 0 – Day 30) post vaccination period are provided in this section.

Table 25 presents the percentage of subjects reporting the occurrence of unsolicited AEs classified by MedDRA SOC and PT during the 31-day (Day 0 – Day 30) post vaccination period.

Table 26 presents the percentage of subjects reporting unsolicited AEs classified by MedDRA SOC and PT with causal relationship to vaccination within the 31-day (Day 0 – Day 30) post vaccination period.

Table 27 presents the percentage of subjects with grade "3" unsolicited AEs classified by MedDRA SOC and PT within the 31-day (Day 0 – Day 30) post vaccination period.

Supplement 92 presents the percentage of doses with unsolicited AEs classified by MedDRA SOC and PT within the 31-day (Day 0 – Day 30) post vaccination period.

Supplement 93 presents the percentage of doses with unsolicited AEs classified by MedDRA SOC and PT with causal relationship to vaccination within the 31-day (Day 0 – Day 30) post vaccination period.

Supplement 94 presents the percentage of doses with grade "3" unsolicited AEs classified by MedDRA SOC and PT within the 31-day (Day 0 – Day 30) post vaccination period.

- The percentage of subjects with report of at least one unsolicited AE classified by MedDRA SOC and PT was 54.9% in the HRV group and 56.0% in the placebo group.
- Unsolicited AEs assessed as causally related to vaccination were reported for 1.0% of the subjects in the HRV group and 0.8% of the subjects in the placebo group.
- The percentage of subjects with report of at least one grade "3" unsolicited AE classified by MedDRA SOC and PT was 2.8% in the HRV group and 3.5% in the placebo group.

Table 25 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		279	54.9	50.5	59.3	144	56.0	49.7	62.2
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Congenital, familial and genetic disorders (10010331)	Atrial septal defect (10003664)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Hydrocele (10020488)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Ear pruritus (10052138)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Otorrhoea (10033101)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
Eye disorders (10015919)	Conjunctivitis (10010741)	18	3.5	2.1	5.5	5	1.9	0.6	4.5
	Eye discharge (10015915)	11	2.2	1.1	3.8	6	2.3	0.9	5.0
	Ocular hyperaemia (10030041)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
Gastrointestinal disorders (10017947)	Anal fissure (10002153)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Constipation (10010774)	16	3.1	1.8	5.1	11	4.3	2.2	7.5
	Diarrhoea (10012735)	4	0.8	0.2	2.0	2	0.8	0.1	2.8
	Epulis (10057974)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Flatulence (10016766)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Gastrointestinal disorder (10017944)	3	0.6	0.1	1.7	4	1.6	0.4	3.9
	Haematochezia (10018836)	7	1.4	0.6	2.8	2	0.8	0.1	2.8
	Inguinal hernia (10022016)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Vomiting (10047700)	8	1.6	0.7	3.1	3	1.2	0.2	3.4
General disorders and administration site conditions (10018065)	Inflammation (10061218)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Irritability (10022998)	3	0.6	0.1	1.7	1	0.4	0.0	2.1
	Pyrexia (10037660)	5	1.0	0.3	2.3	7	2.7	1.1	5.5
Hepatobiliary disorders (10019805)	Hepatic failure (10019663)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Hepatic function abnormal (10019670)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Infections and infestations (10021881)	Adenovirus infection (10060931)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Bronchiolitis (10006448)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Bronchitis (10006451)	10	2.0	0.9	3.6	9	3.5	1.6	6.5

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Candidiasis (10007152)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Eczema impetiginous (10051890)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Exanthema subitum (10015586)	5	1.0	0.3	2.3	0	0.0	0.0	1.4
	Fungal skin infection (10017543)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Gastroenteritis (10017888)	4	0.8	0.2	2.0	0	0.0	0.0	1.4
	Hand-foot-and-mouth disease (10019113)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Herpangina (10019936)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Hordeolum (10020377)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Impetigo (10021531)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Influenza (10022000)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Nasopharyngitis (10028810)	31	6.1	4.2	8.6	13	5.1	2.7	8.5
	Omphalitis (10030306)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Oral candidiasis (10030963)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Otitis externa (10033072)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Otitis media (10033078)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
	Pertussis (10034738)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
	Pharyngitis (10034835)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Pneumonia (10035664)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Respiratory syncytial virus bronchiolitis (10038718)	4	0.8	0.2	2.0	1	0.4	0.0	2.1
	Respiratory syncytial virus infection (10061603)	6	1.2	0.4	2.6	1	0.4	0.0	2.1
	Rhinitis (10039083)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Trichophytosis (10067409)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Upper respiratory tract infection (10046306)	50	9.8	7.4	12.8	25	9.7	6.4	14.0
	Urinary tract infection (10046571)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Varicella (10046980)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
Injury, poisoning and procedural complications (10022117)	Arthropod bite (10003399)	3	0.6	0.1	1.7	3	1.2	0.2	3.4
	Arthropod sting (10003402)	0	0.0	0.0	0.7	1	0.4	0.0	2.1

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Contusion (10050584)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Extradural haematoma (10015769)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Thermal burn (10053615)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Metabolism and nutrition disorders (10027433)	Weight gain poor (10047897)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Musculoskeletal and connective tissue disorders (10028395)	Muscular weakness (10028372)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Musculoskeletal chest pain (10050819)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Musculoskeletal pain (10028391)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Somnolence (10041349)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Psychiatric disorders (10037175)	Nightmare (10029412)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Cough (10011224)	13	2.6	1.4	4.3	10	3.9	1.9	7.0
	Dysphonia (10013952)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Epistaxis (10015090)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Nasal congestion (10028735)	6	1.2	0.4	2.6	3	1.2	0.2	3.4
	Rhinorrhoea (10039101)	19	3.7	2.3	5.8	21	8.2	5.1	12.2
	Sneezing (10041232)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Upper airway obstruction (10067775)	4	0.8	0.2	2.0	2	0.8	0.1	2.8
	Upper respiratory tract inflammation (10049590)	33	6.5	4.5	9.0	16	6.2	3.6	9.9
Skin and subcutaneous tissue disorders (10040785)	Acne (10000496)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Asteatosis (10058130)	5	1.0	0.3	2.3	2	0.8	0.1	2.8
	Dermatitis (10012431)	0	0.0	0.0	0.7	3	1.2	0.2	3.4
	Dermatitis atopic (10012438)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Dermatitis contact (10012442)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Dermatitis diaper (10012444)	16	3.1	1.8	5.1	11	4.3	2.2	7.5
	Dry skin (10013786)	12	2.4	1.2	4.1	5	1.9	0.6	4.5
	Eczema (10014184)	72	14.2	11.3	17.5	29	11.3	7.7	15.8
	Eczema asteatotic (10014190)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
	Eczema infantile (10014198)	11	2.2	1.1	3.8	3	1.2	0.2	3.4

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
	Heat rash (10019343)	18	3.5	2.1	5.5	0	0.0	0.0	1.4
	Intertrigo (10022622)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Pruritus (10037087)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Rash (10037844)	7	1.4	0.6	2.8	3	1.2	0.2	3.4
	Rash vesicular (10037898)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Seborrhoeic dermatitis (10039793)	7	1.4	0.6	2.8	2	0.8	0.1	2.8
	Urticaria (10046735)	3	0.6	0.1	1.7	1	0.4	0.0	2.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 26 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		5	1.0	0.3	2.3	2	0.8	0.1	2.8
Gastrointestinal disorders (10017947)	Constipation (10010774)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
	Gastrointestinal disorder (10017944)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Haematochezia (10018836)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Vomiting (10047700)	1	0.2	0.0	1.1	0	0.0	0.0	1.4

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 27 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		14	2.8	1.5	4.6	9	3.5	1.6	6.5
Gastrointestinal disorders (10017947)	Inguinal hernia (10022016)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Vomiting (10047700)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Hepatobiliary disorders (10019805)	Hepatic failure (10019663)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Infections and infestations (10021881)	Bronchitis (10006451)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Eczema impetiginous (10051890)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Gastroenteritis (10017888)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Influenza (10022000)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Nasopharyngitis (10028810)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Pneumonia (10035664)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Respiratory syncytial virus bronchiolitis (10038718)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Upper respiratory tract infection (10046306)	2	0.4	0.0	1.4	3	1.2	0.2	3.4
	Urinary tract infection (10046571)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Upper respiratory tract inflammation (10049590)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis diaper (10012444)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Eczema (10014184)	1	0.2	0.0	1.1	1	0.4	0.0	2.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

8.3. Serious adverse events

The serious adverse event (SAE) Summary Table(s) are in Section 13.1 and the SAE CIOMS are in Section 13.2.

Table 28 presents the percentage of subjects with SAEs classified by MedDRA SOC and PT during the study period.

- During the entire study period, at least one SAE was reported for 14.2% of subjects in the HRV group and for 17.1% of subjects in the placebo group.
- During the entire study period, majority of the SAEs were classified under SOC MedDRA PT for "Bronchitis" (14 subjects in the HRV group and none in the placebo group), "Pneumonia" (12 subjects in the HRV group and 4 subjects in the placebo group) and "Gastroenteritis" (11 subjects in the HRV group and 2 subjects in the placebo group).

Table 28 Percentage of subjects with SAEs classified by MedDRA Primary System Organ Class and Preferred Term during the study period (Total vaccinated cohort)

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		72	14.2	11.3	17.5	44	17.1	12.7	22.3
Blood and lymphatic system disorders (10005329)	Aplasia pure red cell (10002965)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Iron deficiency anaemia (10022972)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
Congenital, familial and genetic disorders (10010331)	Cryptorchism (10011498)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Eye disorders (10015919)	Conjunctivitis (10010741)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Gastrointestinal disorders (10017947)	Colitis (10009887)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Diarrhoea (10012735)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Enteritis (10014866)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Enterocolitis (10014893)	2	0.4	0.0	1.4	1	0.4	0.0	2.1
	Gastrointestinal disorder (10017944)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
	Haematochezia (10018836)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Inguinal hernia (10022016)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
General disorders and administration site conditions (10018065)	Pyrexia (10037660)	3	0.6	0.1	1.7	1	0.4	0.0	2.1
Hepatobiliary disorders (10019805)	Hepatic failure (10019663)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Hepatic function abnormal (10019670)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
Infections and infestations (10021881)	Acute tonsillitis (10001093)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Adenovirus infection (10060931)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
	Bacteraemia (10003997)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Bacterial infection (10060945)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Bronchitis (10006451)	14	2.8	1.5	4.6	0	0.0	0.0	1.4
	Bronchopneumonia (10006469)	2	0.4	0.0	1.4	2	0.8	0.1	2.8

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Cellulitis (10007882)	0	0.0	0.0	0.7	2	0.8	0.1	2.8
	Croup infectious (10011416)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Enterocolitis viral (10061841)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Erythema infectiosum (10015214)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Exanthema subitum (10015586)	3	0.6	0.1	1.7	2	0.8	0.1	2.8
	Gastroenteritis (10017888)	11	2.2	1.1	3.8	2	0.8	0.1	2.8
	Gastroenteritis rotavirus (10017913)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
	Gastroenteritis viral (10017918)	1	0.2	0.0	1.1	1	0.4	0.0	2.1
	Influenza (10022000)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
	Laryngitis (10023874)	2	0.4	0.0	1.4	0	0.0	0.0	1.4
	Nasopharyngitis (10028810)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Otitis media (10033078)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Otitis media acute (10033079)	1	0.2	0.0	1.1	3	1.2	0.2	3.4
	Pertussis (10034738)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Pharyngitis (10034835)	5	1.0	0.3	2.3	3	1.2	0.2	3.4
	Pneumonia (10035664)	12	2.4	1.2	4.1	4	1.6	0.4	3.9
	Pneumonia respiratory syncytial viral (10035732)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Respiratory syncytial virus bronchiolitis (10038718)	6	1.2	0.4	2.6	2	0.8	0.1	2.8
	Respiratory syncytial virus infection (10061603)	5	1.0	0.3	2.3	3	1.2	0.2	3.4
	Sinusitis (10040753)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Subcutaneous abscess (10042343)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Tonsillitis (10044008)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Upper respiratory tract infection (10046306)	4	0.8	0.2	2.0	1	0.4	0.0	2.1
	Urinary tract infection (10046571)	2	0.4	0.0	1.4	2	0.8	0.1	2.8
Injury, poisoning and procedural complications (10022117)	Contusion (10050584)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Skull fracture (10061365)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Subdural haematoma (10042361)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Metabolism and nutrition disorders (10027433)	Dehydration (10012174)	3	0.6	0.1	1.7	1	0.4	0.0	2.1

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Weight gain poor (10047897)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Musculoskeletal and connective tissue disorders (10028395)	Arthritis (10003246)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Fibroma (10016629)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Neoplasm (10028980)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Teratoma (10043276)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.2	0.0	1.1	2	0.8	0.1	2.8
	Febrile convulsion (10016284)	4	0.8	0.2	2.0	1	0.4	0.0	2.1
	Status epilepticus (10041962)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Subarachnoid haemorrhage (10042316)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Psychiatric disorders (10037175)	Breath holding (10006322)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Respiratory, thoracic and mediastinal disorders (10038738)	Adenoidal hypertrophy (10001229)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
	Asthma (10003553)	5	1.0	0.3	2.3	3	1.2	0.2	3.4
	Rhinorrhoea (10039101)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Upper respiratory tract inflammation (10049590)	0	0.0	0.0	0.7	1	0.4	0.0	2.1
Vascular disorders (10047065)	Kawasaki's disease (10023320)	1	0.2	0.0	1.1	1	0.4	0.0	2.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

8.3.1. Fatal events

There were no fatal events reported during the study.

8.3.2. Non-fatal events

Supplement 95 presents the listing of SAEs reported from Dose 1 up to Visit 5.

- A total of 184 SAEs were reported for 116 subjects (72 subjects in the HRV group and 44 subjects in the placebo group) from Dose 1 up to Visit 5. None of the SAEs were assessed to be causally related to vaccination.

8.4. Adverse events leading to premature discontinuation of study vaccine and/or study

Supplement 96 presents the percentage of subjects with AEs (serious and non-serious) leading to drop out classified by MedDRA SOC and PT during the entire study period.

[redacted] This medical condition developed 20 days after receiving Dose 2 and the randomisation code was broken. The investigator initially considered the SAE to be causally related to vaccination. However, after unblinding and further investigation, this SAE was not considered by the investigator to be causally related to vaccination. Hepatic insufficiency was caused by neonatal intrahepatic cholestasis due to Citrin deficiency. This SAE was ongoing at the time of study end.

[redacted] This subject experienced the AE 38 days after receiving Dose 2 of placebo. The AE lasted only for a day and the subject was withdrawn from the study after Visit 3. The AE was not considered by the investigator to be causally related to vaccination.

8.5. Concomitant medications/vaccinations

Refer to Study report 107625 (Rota-056) for details on concomitant medications/vaccinations.

8.6. Important safety information received after the database freeze date

There was no significant safety data received after the database freeze date for this study.

8.7. Safety conclusions

- The incidence of unsolicited symptoms was similar in the HRV group and placebo group.
- There was no evidence of a clinically meaningful difference between the HRV group and placebo group for SAEs reported from Dose 1 up to Visit 5.

9. DISCUSSION AND OVERALL CONCLUSIONS

9.1. Discussion

Rota-056 was the first study that was conducted to assess the efficacy, immunogenicity reactogenicity and safety of the HRV vaccine in Japanese infants aged approximately 2 months at the time of the first vaccination. The study was designed to analyse the efficacy of the vaccine against RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the follow up period from 2 weeks post Dose 2 up to 2 years of age. The protocol allowed for efficacy analysis when 28 RV GE leading

to medical intervention and caused by the circulating wild-type RV strains was identified and final analyses up to the data lock point of 31 March 2009 was performed and presented in the primary study report [GlaxoSmithKline Biologicals' Study Report 107625 (Rota-056)].

Two oral doses of the HRV vaccine were found to be highly efficacious in preventing any RV GE leading to medical intervention (vaccine efficacy: 79.3% [95% CI: 60.5%; 89.8%]) and severe RV GE leading to medical intervention (vaccine efficacy: 91.6% [95% CI: 62.4%; 99.1%]) for the efficacy period starting from 2 weeks post Dose 2 up to Visit 5 (i.e. first year of life). Efficacy results of the efficacy follow-up period from 2 weeks post dose 2 up to Visit 4 (i.e. second year of life) were in line with high vaccine efficacy against any RV GE leading to medical intervention (79.1% [95% CI: 36.2%; 94.2%]) and against severe RV GE leading to medical intervention (87.4% [95% CI: -26.8%; 99.7%]).

G1P[8] and G3P[8] were the most prominent RV types circulating during the efficacy follow-up period. Vaccine efficacy against any RV GE episodes caused by G1 wild type and G3 type leading to medical intervention were 84.6% [95% CI: 50.0%; 96.3%] and 88.4% [95% CI: 57.8%; 97.9%], respectively. Similarly, excellent protection was shown against severe RV GE caused by G1 wild-type RV leading to medical intervention (vaccine efficacy: 91.6% [95% CI: 31.0%; 99.8%] and G3 type (vaccine efficacy: 100.0% [95% CI: 24.0%; 100.0%]). However, low incidence of G2, G4 and G9 types precluded demonstration of statistical significance against these types. Efficacy against circulating non-G1 types has been demonstrated in other clinical studies [Ruiz Palacios, 2006; Vesikari, 2007].

The incidence of severe RV GE leading to medical intervention in the placebo group was lower in the follow-up period during the first year of life (1.6%) than the follow up period during second year of life (3.3%). Significant protection was demonstrated both in the first year (vaccine efficacy: 87.4%) and in the second year of life (vaccine efficacy: 93.8%).

The safety results observed in this study are congruent with the safety profile of the HRV vaccine with no concerns raised. A total of 14 subjects in the HRV group had a report of Bronchitis while there were none reported in the placebo group. This SAE has been assessed in previous clinical trials where no statistical difference has been observed between the HRV group and placebo group [GlaxoSmithKline Biologicals' Study Report 102247 (Rota-037)]. None of the SAEs reported were considered to be causally related to vaccination. There were no fatal cases in the study.

Overall, two oral doses of the HRV vaccine has found to be highly efficacious in Japanese infants and introducing the vaccine in the immunisation programme in Japan is expected to be beneficial in reducing the disease burden.

9.2. Overall conclusions

Efficacy:

- Two doses of the HRV vaccine were found to be highly effective against any RV GE caused by wild-type RV leading to medical intervention during the efficacy period starting from 2 weeks post Dose 2 up to Visit 5 with a vaccine efficacy of 79.3% [95% CI: 60.5%; 89.8%] thereby meeting the primary objective of the study.
- Two doses of HRV vaccine were found to be highly efficacious against:
- Severe RV GE caused by the circulating wild-type RV leading to medical intervention with a vaccine efficacy of 91.6% [95% CI: 62.4%; 99.1%].
  - Any RV GE episodes caused by G1 wild-type RV leading to medical intervention with a vaccine efficacy of 84.6% [95% CI: 50.0%; 96.3%].
  - Severe RV GE leading to medical intervention caused by G1 wild-type RV with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
  - Any RV GE leading to medical intervention caused by non-G1 RV type with a vaccine efficacy of 76.1% [95% CI: 47.0%; 89.9%].
  - Severe RV GE leading to medical intervention caused by non-G1 RV types with a vaccine efficacy of 91.6% [95% CI: 31.0%; 99.8%].
  - There were very few reports of hospitalisation due to RV GE leading to medical intervention (1 subject in the HRV group and 2 subjects in the placebo group).
- During the period starting from Dose 1 up to Visit 5, vaccine efficacy against any and severe RV GE leading to medical intervention caused by wild-type RV was 80.3% [95% CI: 62.6%; 90.2%] and 92.2% [95% CI: 65.6%; 99.1%], respectively.

Safety:

- The incidence of unsolicited symptoms was similar in the HRV group and placebo group.
- There was no evidence of a clinically meaningful difference between the HRV group and placebo group for SAEs reported from Dose 1 up to Visit 5.

10. SUPPLEMENTS

Supplement 1 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at Visit 4 (Total vaccinated cohort)

	HRV	Placebo	Total
Number of subjects vaccinated	508	257	765
Number of subjects completed	492	247	739
Number of subjects withdrawn	16	10	26
Reasons for withdrawal :			
Serious Adverse Event	1	0	1
Non-serious adverse event	0	1	1
Protocol violation	0	1	1
Consent withdrawal (not due to an adverse event)	9	3	12
Migrated/moved from study area	6	2	8
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	3	3
Others	0	0	0

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit

Supplement 2 Summary of demographic characteristics (ATP cohort for efficacy during the period from Visit 4 to Visit 5)

		HRV N = 487		Placebo N = 243		Total N = 730	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at Dose 1 of HRV/Placebo	Mean	7.7	-	7.7	-	7.7	-
	SD	1.93	-	2.03	-	1.96	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	6	-	6	-
	Maximum	14	-	14	-	14	-
Age (weeks) at Dose 2 of HRV/Placebo	Mean	12.7	-	12.7	-	12.7	-
	SD	2.01	-	2.15	-	2.05	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	19	-	20	-	20	-
Age (months) at Visit 4/ Last contact if Visit 4 is not performed	Mean	11.5	-	11.5	-	11.5	-
	SD	0.51	-	0.51	-	0.51	-
	Median	12.0	-	11.0	-	12.0	-
	Minimum	11	-	11	-	11	-
	Maximum	13	-	13	-	13	-
Age (months) at Visit 5/ Last contact if Visit 5 is not performed	Mean	23.4	-	23.4	-	23.4	-
	SD	1.08	-	0.82	-	1.00	-
	Median	23.0	-	23.0	-	23.0	-
	Minimum	13	-	14	-	13	-
	Maximum	25	-	25	-	25	-
Gender	Female	221	45.4	128	52.7	349	47.8
	Male	266	54.6	115	47.3	381	52.2
Race	Asian - Japanese heritage	487	100	243	100	730	100

N = total number of subjects in each group
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

Supplement 3 Summary of demographic characteristics (Total vaccinated cohort)

		HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at Dose 1 of HRV/Placebo	Mean	7.7	-	7.7	-	7.7	-
	SD	1.99	-	2.05	-	2.01	-
	Median	7.0	-	7.0	-	7.0	-
	Minimum	6	-	5	-	5	-
	Maximum	14	-	14	-	14	-
Age (weeks) at Dose 2 of HRV/Placebo	Mean	12.7	-	12.7	-	12.7	-
	SD	2.03	-	2.18	-	2.08	-
	Median	12.0	-	12.0	-	12.0	-
	Minimum	10	-	10	-	10	-
	Maximum	19	-	20	-	20	-
	Unknown*	9	-	7	-	16	-
Age (months) at Visit 4/ Last contact if Visit 4 is not performed	Mean	11.4	-	11.3	-	11.4	-
	SD	1.12	-	1.33	-	1.19	-
	Median	12.0	-	11.0	-	11.0	-
	Minimum	1	-	2	-	1	-
	Maximum	13	-	13	-	13	-
Age (months) at Visit 5/ Last contact if Visit 5 is not performed	Mean	22.9	-	22.7	-	22.8	-
	SD	3.07	-	3.55	-	3.23	-
	Median	23.0	-	23.0	-	23.0	-
	Minimum	1	-	2	-	1	-
	Maximum	25	-	25	-	25	-
Gender	Female	229	45.1	134	52.1	363	47.5
	Male	279	54.9	123	47.9	402	52.5
Race	Asian - Japanese heritage	508	100	257	100	765	100

N = total number of subjects in each group
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
*These subjects didn't receive dose 2 of HRV/Placebo

Supplement 4 Subjects unblinded before database lock (01 MAR 2010) (Total vaccinated cohort)

Group	Subject number	Date of unblinding	Previous dose	Day of onset	Reason
[redacted]					

Day of onset: relative to previous dose administered (administration day is day 0)

Supplement 5 Percentage of GE episodes leading to medical intervention with no available stool results from 2 weeks post Dose 2 up to Visit 5 (ATP cohort for efficacy)

Category	HRV N'=313		Placebo N'=170	
	n	%	n	%
No stool results available	23	7.3	6	3.5
no stools collected	12	3.8	0	0.0
stools collected but no results available	11	3.5	6	3.5

HRV = HRV group
Placebo = Placebo group
N = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 6 Percentage of subjects with RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5, by G type and P type (ATP cohort for efficacy)

	HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	n	%	n	%	n	%
Any	14	2.8	34	13.6	48	6.4
G1WT	4	0.8	13	5.2	17	2.3
G2	1	0.2	2	0.8	3	0.4
G3	3	0.6	13	5.2	16	2.1
G4	1	0.2	1	0.4	2	0.3
G9	5	1.0	5	2.0	10	1.3
P4	1	0.2	2	0.8	3	0.4
P8 wild type	13	2.6	32	12.8	45	6.0

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 7 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5, by G type and P type (ATP cohort for efficacy)

	HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	n	%	n	%	n	%
Any	2	0.4	12	4.8	14	1.9
G1WT	1	0.2	6	2.4	7	0.9
G3	0	0.0	4	1.6	4	0.5
G9	1	0.2	2	0.8	3	0.4
P8 wild type	2	0.4	12	4.8	14	1.9

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 8 Number of RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 5, by G and P type (ATP cohort for efficacy)

Type	HRV		Placebo	
	n	%	n	%
Any	14	100.0	34	100.0
G1WT+P8WT	4	28.57	13	38.24
G2+P4	1	7.14	2	5.88
G3+P8WT	3	21.43	13	38.24
G4+P8WT	1	7.14	1	2.94
G9+P8WT	5	35.71	5	14.71

HRV = HRV group
Placebo = Placebo group
n (%) = number (percentage) of RV GE episodes reporting the specified RV type in each group, among all RV GE episodes reported from 2 weeks post dose 2 up to visit 5
Any = any specified symptom reported, regardless of the RV type

Supplement 9 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 5 (ATP cohort for efficacy)

		HRV N' = 14		Placebo N' = 34	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	7.8	-	9.1	-
	SD	4.1	-	3.4	-
	Median	7.5	-	9.0	-
	Minimum	4.0	-	2.0	-
	Maximum	20.0	-	16.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	10	71.4	25	73.5
	5	2	14.3	5	14.7
	more than 5 days	2	14.3	4	11.8
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	1	7.1	6	17.6
	4 to 5	6	42.9	9	26.5
	more than 5	7	50.0	19	55.9
Duration of vomiting (days)	0 day	8	57.1	9	26.5
	1 day	4	28.6	13	38.2
	2 days	1	7.1	8	23.5
	more than 2 days	1	7.1	4	11.8
Max number of episodes of vomiting /day	0	8	57.1	9	26.5
	1	3	21.4	7	20.6
	2 to 4	1	7.1	11	32.4
	more than 4	2	14.3	7	20.6
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	2	5.9
	37.1 to 38.4°C	6	42.9	14	41.2
	38.5 to 38.9°C	5	35.7	3	8.8
	more than 38.9°C	3	21.4	15	44.1
Treatment	none	10	71.4	22	64.7
	rehydration	3	21.4	10	29.4
	hospitalization	1	7.1	2	5.9
Dehydration	none	12	85.7	30	88.2
	1 to 5%	1	7.1	1	2.9
	more than 5 %	1	7.1	3	8.8

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 10 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 5 – by G1WT type (ATP cohort for efficacy)

		HRV N' = 4		Placebo N' = 13	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	8.0	-	10.0	-
	SD	2.2	-	3.8	-
	Median	7.5	-	10.0	-
	Minimum	6.0	-	2.0	-
	Maximum	11.0	-	16.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	3	75.0	10	76.9
	5	1	25.0	3	23.1
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	4	30.8
	4 to 5	2	50.0	1	7.7
	more than 5	2	50.0	8	61.5
Duration of vomiting (days)	0 day	2	50.0	2	15.4
	1 day	2	50.0	5	38.5
	2 days	0	0.0	2	15.4
	more than 2 days	0	0.0	4	30.8
Max number of episodes of vomiting /day	0	2	50.0	2	15.4
	1	1	25.0	2	15.4
	2 to 4	1	25.0	5	38.5
	more than 4	0	0.0	4	30.8
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	7.7
	37.1 to 38.4°C	0	0.0	1	7.7
	38.5 to 38.9°C	3	75.0	2	15.4
	more than 38.9°C	1	25.0	9	69.2
Treatment	none	3	75.0	10	76.9
	rehydration	1	25.0	2	15.4
	hospitalization	0	0.0	1	7.7
Dehydration	none	3	75.0	12	92.3
	1 to 5%	1	25.0	0	0.0
	more than 5 %	0	0.0	1	7.7

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 11 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 5 – by G4 type (ATP cohort for efficacy)

		HRV N' = 1		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	4.0	-	8.0	-
	SD	0.0	-	0.0	-
	Median	4.0	-	8.0	-
	Minimum	4.0	-	8.0	-
	Maximum	4.0	-	8.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	100	0	0.0
	5	0	0.0	1	100
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	0	0.0
	more than 5	0	0.0	1	100
Duration of vomiting (days)	0 day	1	100	1	100
	1 day	0	0.0	0	0.0
	2 days	0	0.0	0	0.0
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	1	100	1	100
	1	0	0.0	0	0.0
	2 to 4	0	0.0	0	0.0
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	100	0	0.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	1	100
Treatment	none	1	100	1	100
	rehydration	0	0.0	0	0.0
	hospitalization	0	0.0	0	0.0
Dehydration	none	1	100	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 12 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 5 – by G2 type (ATP cohort for efficacy)

		HRV N' = 1		Placebo N' = 2	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	9.0	-	6.5	-
	SD	0.0	-	0.7	-
	Median	9.0	-	6.5	-
	Minimum	9.0	-	6.0	-
	Maximum	9.0	-	7.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	2	100
	5	0	0.0	0	0.0
	more than 5 days	1	100	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	2	100
	more than 5	0	0.0	0	0.0
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	0	0.0	1	50.0
	2 days	1	100	1	50.0
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	1	100	1	50.0
	2 to 4	0	0.0	1	50.0
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	50.0
	37.1 to 38.4°C	1	100	1	50.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	0	0.0
Treatment	none	1	100	2	100
	rehydration	0	0.0	0	0.0
	hospitalization	0	0.0	0	0.0
Dehydration	none	1	100	2	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 13 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 5 – by G3 type (ATP cohort for efficacy)

		HRV N' = 3		Placebo N' = 13	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	4.7	-	8.8	-
	SD	1.2	-	3.5	-
	Median	4.0	-	7.0	-
	Minimum	4.0	-	5.0	-
	Maximum	6.0	-	15.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	3	100	9	69.2
	5	0	0.0	1	7.7
	more than 5 days	0	0.0	3	23.1
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	1	33.3	1	7.7
	4 to 5	2	66.7	3	23.1
	more than 5	0	0.0	9	69.2
Duration of vomiting (days)	0 day	3	100	4	30.8
	1 day	0	0.0	6	46.2
	2 days	0	0.0	3	23.1
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	3	100	4	30.8
	1	0	0.0	3	23.1
	2 to 4	0	0.0	4	30.8
	more than 4	0	0.0	2	15.4
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	2	66.7	9	69.2
	38.5 to 38.9°C	0	0.0	1	7.7
	more than 38.9°C	1	33.3	3	23.1
Treatment	none	2	66.7	8	61.5
	rehydration	1	33.3	4	30.8
	hospitalization	0	0.0	1	7.7
Dehydration	none	3	100	11	84.6
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	2	15.4

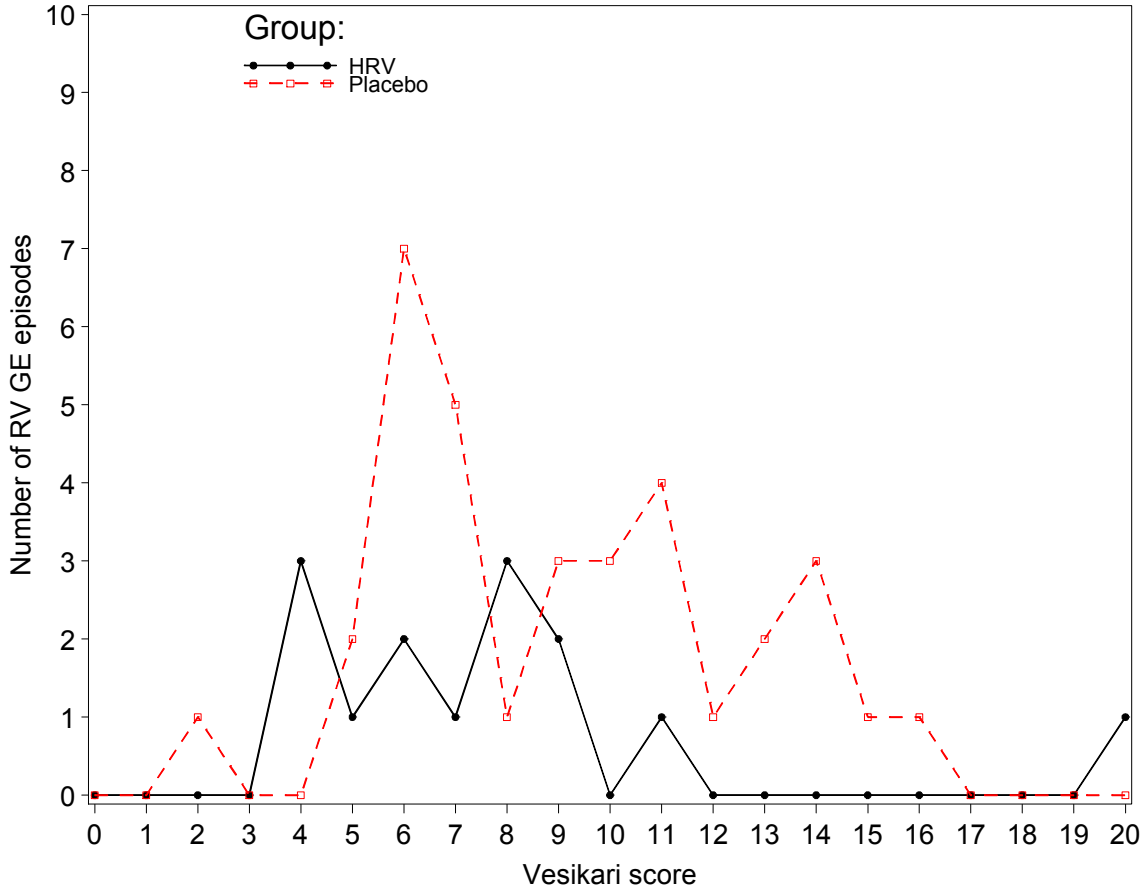
N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 14 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 5 – by G9 type (ATP cohort for efficacy)

		HRV N' = 5		Placebo N' = 5	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	10.0	-	8.6	-
	SD	5.8	-	3.2	-
	Median	8.0	-	7.0	-
	Minimum	5.0	-	6.0	-
	Maximum	20.0	-	13.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	3	60.0	4	80.0
	5	1	20.0	0	0.0
	more than 5 days	1	20.0	1	20.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	1	20.0
	4 to 5	0	0.0	3	60.0
	more than 5	5	100	1	20.0
Duration of vomiting (days)	0 day	2	40.0	2	40.0
	1 day	2	40.0	1	20.0
	2 days	0	0.0	2	40.0
	more than 2 days	1	20.0	0	0.0
Max number of episodes of vomiting /day	0	2	40.0	2	40.0
	1	1	20.0	1	20.0
	2 to 4	0	0.0	1	20.0
	more than 4	2	40.0	1	20.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	2	40.0	3	60.0
	38.5 to 38.9°C	2	40.0	0	0.0
	more than 38.9°C	1	20.0	2	40.0
Treatment	none	3	60.0	1	20.0
	rehydration	1	20.0	4	80.0
	hospitalization	1	20.0	0	0.0
Dehydration	none	4	80.0	4	80.0
	1 to 5%	0	0.0	1	20.0
	more than 5 %	1	20.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 15 Distribution of Vesikari score for RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to Visit 5 (ATP cohort for efficacy)



Supplement 16 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 2 up to Visit 5 (ATP cohort for efficacy)

		HRV N = 498	Placebo N = 250
Characteristics	**Parameters**	**Value**	**Value**
Duration in years	Total	834.58	417.04
	Mean	1.68	1.67
	Minimum	0.09	0.11
	Q1	1.69	1.69
	Median	1.71	1.71
	Q3	1.74	1.74
	Maximum	1.85	1.82

HRV = HRV group
Placebo = Placebo group
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

Supplement 17 Efficacy of the vaccine against any RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to Visit 5 – by Cox method (ATP cohort for efficacy)

				Person-year rate			VE			
Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any										
HRV	498	14	825.12	0.017	0.010	0.029	80.657	63.955	89.620	<0.001
Placebo	250	34	391.85	0.087	0.062	0.121	-	-	-	.
(G1WT)										
HRV	498	4	833.20	0.005	0.002	0.013	84.886	53.646	95.072	<0.001
Placebo	250	13	412.50	0.032	0.018	0.054	-	-	-	.
(Pooled Non-G1)										
HRV	498	10	826.51	0.012	0.007	0.022	77.148	51.472	89.238	<0.001
Placebo	250	21	396.39	0.053	0.035	0.081	-	-	-	.

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine efficacy (Cox regression model)
P-value from Cox regression model to test H0 = (VE=0%) (Y = Time to Event)

Supplement 18 Percentage of subjects reporting any RV GE episodes leading to medical intervention and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 5 (ATP cohort for efficacy)

Group				Person-year rate			Risk difference		
	N	n	T(Year)	n/T	LL	UL	RD	LL	UL
Any RV GE									
HRV	498	14	825.12	0.017	0.01	0.029	0.070	0.042	0.105
Placebo	250	34	391.85	0.087	0.062	0.121	.	.	.
Severe RV GE									
HRV	498	2	833.11	0.002	0.001	0.01	0.027	0.012	0.049
Placebo	250	12	408.57	0.029	0.017	0.052	.	.	.

HRV = HRV group
Placebo = Placebo group
N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(s) in each group
T (Year) = Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T= person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Relative difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner

Supplement 19 Efficacy of the vaccine against severe RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to Visit 5 - by Cox method (ATP cohort for efficacy)

				Person-year rate			VE			
Group	**N**	**n**	**T (year)**	**n/T**	**LL**	**UL**	**%**	**LL**	**UL**	**P-VALUE**
Any										
HRV	498	2	833.11	0.002	0.001	0.010	91.867	63.659	98.180	0.001
Placebo	250	12	408.57	0.029	0.017	0.052	-	-	-	.
(G1WT)										
HRV	498	1	834.38	0.001	0.000	0.009	91.755	31.511	99.007	0.021
Placebo	250	6	414.87	0.014	0.006	0.032	-	-	-	.
(Pooled Non-G1)										
HRV	498	1	833.31	0.001	0.000	0.009	91.786	31.772	99.011	0.021
Placebo	250	6	410.75	0.015	0.007	0.033	-	-	-	.

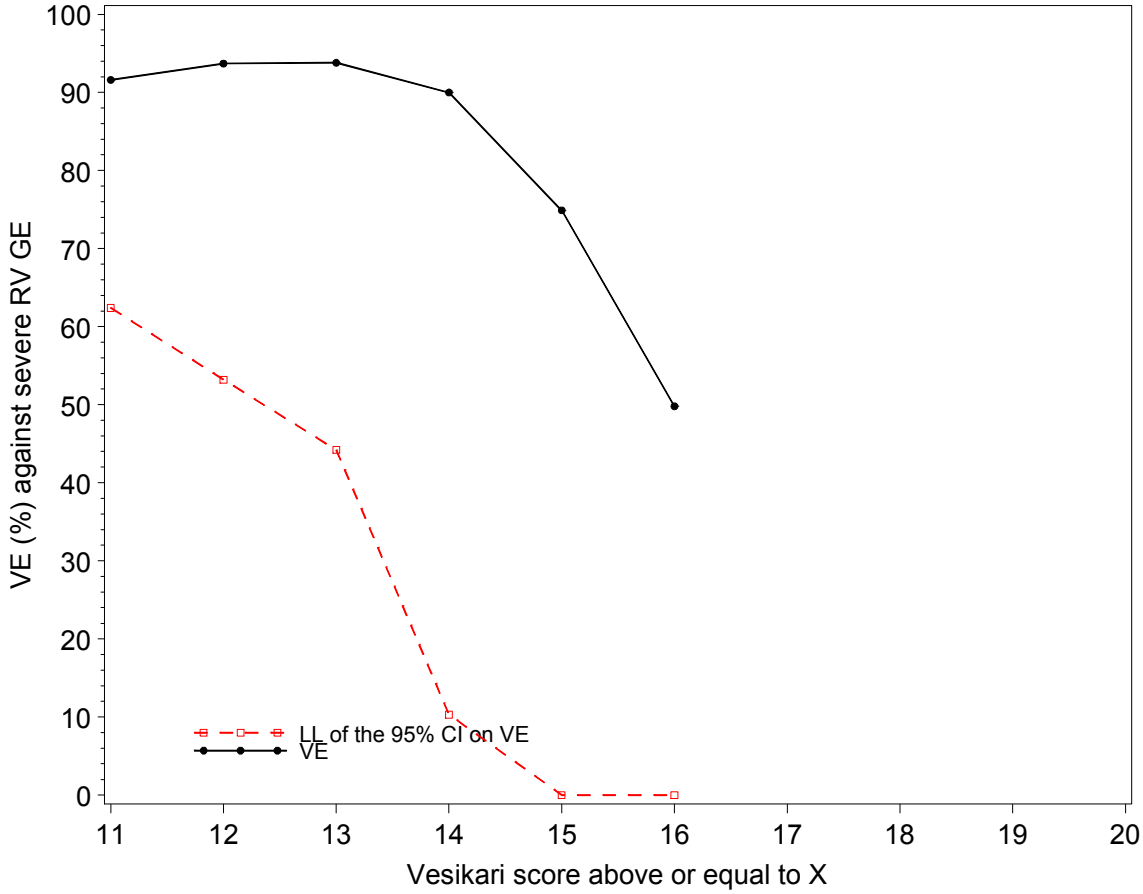
HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine efficacy (Cox regression model)
P-value from Cox regression model to test H0 = (VE=0%) (Y = Time to Event)

Supplement 20 Percentage of subjects reporting severe RV GE episodes leading to medical intervention with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 5 (ATP cohort for efficacy)

				n/N			VE			
Vesikari score	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
≥11	HRV	498	2	0.4	0.0	1.4	91.6	62.4	99.1	<0.001
	Placebo	250	12	4.8	2.5	8.2	-	-	-	-
≥12	HRV	498	1	0.2	0.0	1.1	93.7	53.2	99.9	0.002
	Placebo	250	8	3.2	1.4	6.2	-	-	-	-
≥13	HRV	498	1	0.2	0.0	1.1	92.8	44.2	99.8	0.005
	Placebo	250	7	2.8	1.1	5.7	-	-	-	-
≥14	HRV	498	1	0.2	0.0	1.1	90.0	10.3	99.8	0.036
	Placebo	250	5	2.0	0.7	4.6	-	-	-	-
≥15	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
≥16	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
≥17	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥18	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥19	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥20	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 21 Efficacy of the vaccine against severe RV GE episodes leading to medical intervention with a score greater than or equal to X on the Vesikari scale from 2 weeks post Dose 2 to Visit 5 (ATP cohort for efficacy)



Supplement 22 Percentage of subjects reporting all cause GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	201	40.4	36.0	44.8	9.1	-15.7	28.3	0.453
Placebo	250	111	44.4	38.1	50.8	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 23 Percentage of subjects reporting all cause severe GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	35	7.0	4.9	9.6	32.4	-16.9	60.5	0.169
Placebo	250	26	10.4	6.9	14.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 24 Percentage of subjects hospitalised due to all cause GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	498	16	3.2	1.8	5.2	-33.9	-317.7	50.2	0.717
Placebo	250	6	2.4	0.9	5.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 25 Percentage of GE episodes leading to medical intervention with no available stool results from 2 weeks post Dose 2 up to Visit 4 (ATP cohort for efficacy)

Category	HRV N'=155		Placebo N'=92	
	n	%	n	%
No stool results available	13	8.4	4	4.3
no stools collected	8	5.2	0	0.0
stools collected but no results available	5	3.2	4	4.3

HRV = HRV group
Placebo = Placebo group
N = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 26 Percentage of subjects with RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 4, by G type and P type (ATP cohort for efficacy)

	HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Any	5	1.0	12	4.8	17	2.3
G2	0	0.0	1	0.4	1	0.1
G3	1	0.2	6	2.4	7	0.9
G4	1	0.2	1	0.4	2	0.3
G9	3	0.6	4	1.6	7	0.9
P4	0	0.0	1	0.4	1	0.1
P8 wild type	5	1.0	11	4.4	16	2.1

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 27 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 4, by G type and P type (ATP cohort for efficacy)

	HRV N = 498		Placebo N = 250		Total N = 748	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Any	1	0.2	4	1.6	5	0.7
G3	0	0.0	2	0.8	2	0.3
G9	1	0.2	2	0.8	3	0.4
P8 wild type	1	0.2	4	1.6	5	0.7

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 28 Number of RV GE episodes leading to medical intervention reported from 2 weeks post Dose 2 up to Visit 4 , by G and P type (ATP cohort for efficacy)

Type	HRV		Placebo	
	n	**%**	**n**	**%**
Any	5	100.0	12	100.0
G2+P4	0	0.00	1	8.33
G3+P8WT	1	20.00	6	50.00
G4+P8WT	1	20.00	1	8.33
G9+P8WT	3	60.00	4	33.33

HRV = HRV group
Placebo = Placebo group
n (%) = number (percentage) of RV GE episodes reporting the specified RV type in each group, among all RV GE episodes reported from 2 weeks post dose 2 up to visit 4
Any = any specified symptom reported, regardless of the RV type

Supplement 29 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 4 (ATP cohort for efficacy)

		HRV N' = 5		Placebo N' = 12	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	8.2	-	8.5	-
	SD	6.8	-	3.2	-
	Median	5.0	-	7.0	-
	Minimum	4.0	-	5.0	-
	Maximum	20.0	-	15.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	3	60.0	7	58.3
	5	1	20.0	1	8.3
	more than 5 days	1	20.0	4	33.3
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	1	8.3
	4 to 5	2	40.0	5	41.7
	more than 5	3	60.0	6	50.0
Duration of vomiting (days)	0 day	4	80.0	6	50.0
	1 day	0	0.0	2	16.7
	2 days	0	0.0	4	33.3
	more than 2 days	1	20.0	0	0.0
Max number of episodes of vomiting /day	0	4	80.0	6	50.0
	1	0	0.0	3	25.0
	2 to 4	0	0.0	2	16.7
	more than 4	1	20.0	1	8.3
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	8.3
	37.1 to 38.4°C	3	60.0	6	50.0
	38.5 to 38.9°C	1	20.0	1	8.3
	more than 38.9°C	1	20.0	4	33.3
Treatment	none	3	60.0	6	50.0
	rehydration	1	20.0	5	41.7
	hospitalization	1	20.0	1	8.3
Dehydration	none	4	80.0	10	83.3
	1 to 5%	0	0.0	1	8.3
	more than 5 %	1	20.0	1	8.3

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 30 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 4 – by G4 type (ATP cohort for efficacy)

		HRV N' = 1		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	4.0	-	8.0	-
	SD	0.0	-	0.0	-
	Median	4.0	-	8.0	-
	Minimum	4.0	-	8.0	-
	Maximum	4.0	-	8.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	100	0	0.0
	5	0	0.0	1	100
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	0	0.0
	more than 5	0	0.0	1	100
Duration of vomiting (days)	0 day	1	100	1	100
	1 day	0	0.0	0	0.0
	2 days	0	0.0	0	0.0
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	1	100	1	100
	1	0	0.0	0	0.0
	2 to 4	0	0.0	0	0.0
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	100	0	0.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	1	100
Treatment	none	1	100	1	100
	rehydration	0	0.0	0	0.0
	hospitalization	0	0.0	0	0.0
Dehydration	none	1	100	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 31 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 4 – by G2 type (ATP cohort for efficacy)

		HRV N' = 0		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	0	-	6.0	-
	SD	0	-	0.0	-
	Median	0	-	6.0	-
	Minimum	0	-	6.0	-
	Maximum	0	-	6.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	1	100
	5	0	0.0	0	0.0
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	0	0.0	1	100
	more than 5	0	0.0	0	0.0
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	0	0.0	0	0.0
	2 days	0	0.0	1	100
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	0	0.0	1	100
	2 to 4	0	0.0	0	0.0
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	100
	37.1 to 38.4°C	0	0.0	0	0.0
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	0	0.0
Treatment	none	0	0.0	1	100
	rehydration	0	0.0	0	0.0
	hospitalization	0	0.0	0	0.0
Dehydration	none	0	0.0	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 32 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 4 – by G3 type (ATP cohort for efficacy)

		HRV N' = 1		Placebo N' = 6	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	4.0	-	8.5	-
	SD	0.0	-	3.8	-
	Median	4.0	-	7.0	-
	Minimum	4.0	-	5.0	-
	Maximum	4.0	-	15.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	100	3	50.0
	5	0	0.0	0	0.0
	more than 5 days	0	0.0	3	50.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	2	33.3
	more than 5	0	0.0	4	66.7
Duration of vomiting (days)	0 day	1	100	3	50.0
	1 day	0	0.0	2	33.3
	2 days	0	0.0	1	16.7
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	1	100	3	50.0
	1	0	0.0	2	33.3
	2 to 4	0	0.0	1	16.7
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	100	4	66.7
	38.5 to 38.9°C	0	0.0	1	16.7
	more than 38.9°C	0	0.0	1	16.7
Treatment	none	1	100	4	66.7
	rehydration	0	0.0	1	16.7
	hospitalization	0	0.0	1	16.7
Dehydration	none	1	100	5	83.3
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	1	16.7

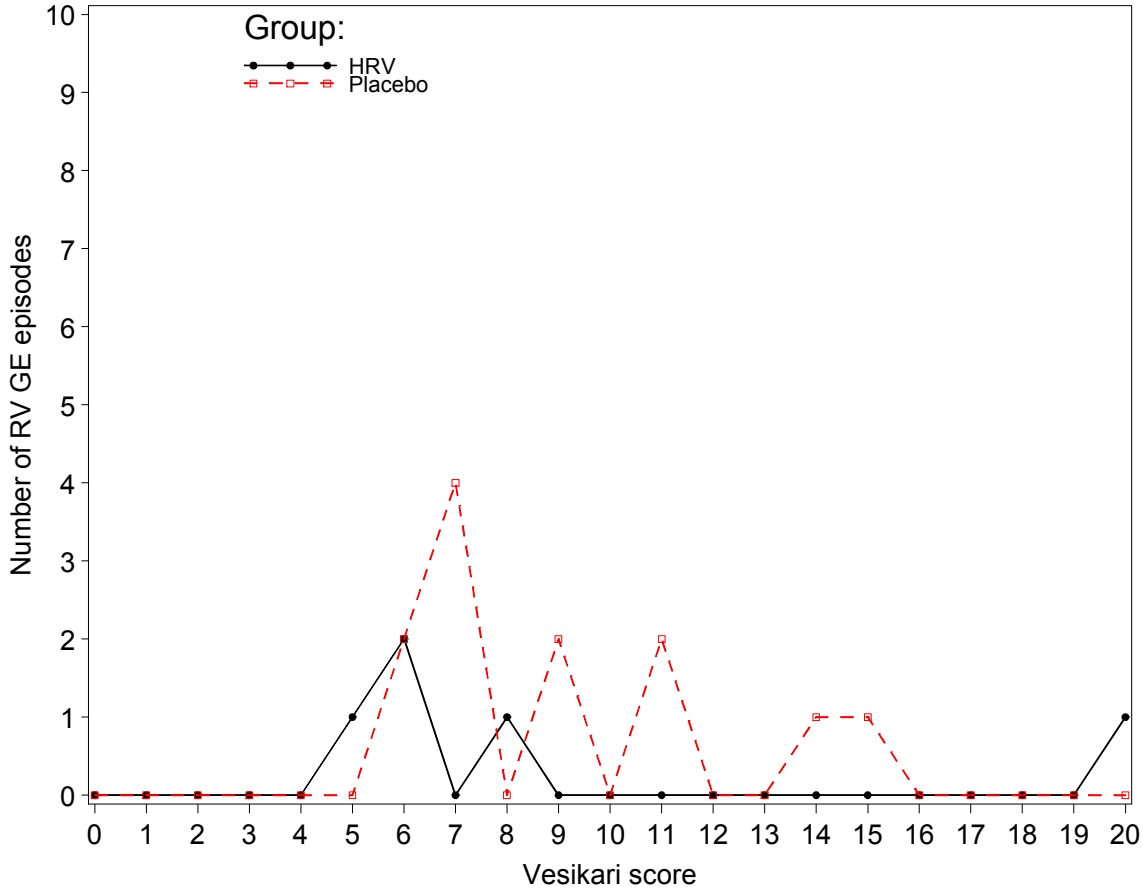
N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 33 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from 2 weeks post Dose 2 to Visit 4 – by G9 type (ATP cohort for efficacy)

		HRV N' = 3		Placebo N' = 4	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	11.0	-	9.3	-
	SD	7.9	-	3.3	-
	Median	8.0	-	9.0	-
	Minimum	5.0	-	6.0	-
	Maximum	20.0	-	13.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	1	33.3	3	75.0
	5	1	33.3	0	0.0
	more than 5 days	1	33.3	1	25.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	1	25.0
	4 to 5	0	0.0	2	50.0
	more than 5	3	100	1	25.0
Duration of vomiting (days)	0 day	2	66.7	2	50.0
	1 day	0	0.0	0	0.0
	2 days	0	0.0	2	50.0
	more than 2 days	1	33.3	0	0.0
Max number of episodes of vomiting /day	0	2	66.7	2	50.0
	1	0	0.0	0	0.0
	2 to 4	0	0.0	1	25.0
	more than 4	1	33.3	1	25.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	33.3	2	50.0
	38.5 to 38.9°C	1	33.3	0	0.0
	more than 38.9°C	1	33.3	2	50.0
Treatment	none	1	33.3	0	0.0
	rehydration	1	33.3	4	100
	hospitalization	1	33.3	0	0.0
Dehydration	none	2	66.7	3	75.0
	1 to 5%	0	0.0	1	25.0
	more than 5 %	1	33.3	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 34 Distribution of Vesikari score for RV GE episodes leading to medical intervention reported from 2 weeks after Dose 2 up to Visit 4 (ATP cohort for efficacy)



Supplement 35 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 2 up to Visit 4 (ATP cohort for efficacy)

		HRV N = 498	Placebo N = 250
Characteristics	**Parameters**	**Value**	**Value**
Duration in years	Total	352.64	175.17
	Mean	0.71	0.70
	Minimum	0.09	0.11
	Q1	0.69	0.69
	Median	0.71	0.71
	Q3	0.74	0.74
	Maximum	0.86	0.79

HRV = HRV group
Placebo = Placebo group
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

Supplement 36 Efficacy of the vaccine against any RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to Visit 4 – by Cox method (ATP cohort for efficacy)

				Person-year rate			VE			
Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
HRV	498	5	351.44	0.014	0.006	0.034	79.834	42.757	92.896	0.003
Placebo	250	12	171.09	0.070	0.040	0.124	-	-	-	.

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine efficacy (Cox regression model)
P-value from Cox regression model to test H0 = (VE=0%) (Y = Time to Event)

Supplement 37 Percentage of subjects reporting any RV GE episodes leading to medical intervention and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 4 (ATP cohort for efficacy)

Group				Person-year rate			Risk difference		
	N	n	T(Year)	n\ T	LL	UL	RD	LL	UL
Any RV GE									
HRV	498	5	351.44	0.014	0.006	0.034	0.056	0.020	0.110
Placebo	250	12	171.09	0.07	0.04	0.124	.	.	.
Severe RV GE									
HRV	498	1	352.37	0.003	0	0.02	0.020	-0.002	0.058
Placebo	250	4	173.99	0.023	0.009	0.061	.	.	.

HRV = HRV group
Placebo = Placebo group
N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(S) in each group
T (Year) = Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T= person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Relative difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner

Supplement 38 Efficacy of the vaccine against severe RV GE episodes leading to medical intervention from 2 weeks after Dose 2 up to Visit 4 - by Cox method (ATP cohort for efficacy)

				Person-year rate			VE			
Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
HRV	498	1	352.37	0.003	0.000	0.020	87.686	-10.148	98.623	0.061
Placebo	250	4	173.99	0.023	0.009	0.061	-	-	-	.

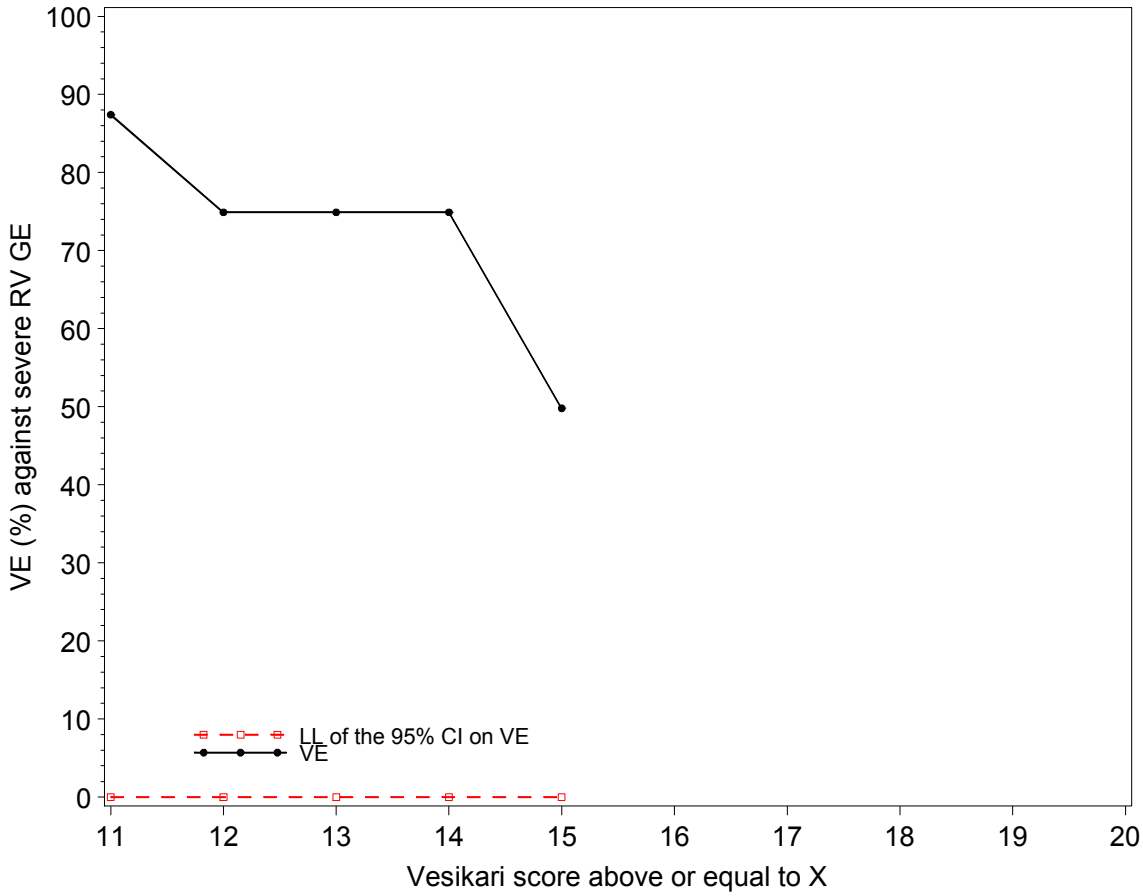
HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T= person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine efficacy (Cox regression model)
P-value from Cox regression model to test H0 = (VE=0%) (Y = Time to Event)

Supplement 39 Percentage of subjects reporting severe RV GE episodes leading to medical intervention with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 4 (ATP cohort for efficacy)

				n/N			VE			
Vesikari score	Group	N	n	%	LL	UL	%	LL	UL	P-value
≥11	HRV	498	1	0.2	0.0	1.1	87.4	-26.8	99.7	0.091
	Placebo	250	4	1.6	0.4	4.0	-	-	-	-
≥12	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
≥13	HRV	498	1	0.2	0.0	1.1	74.9	-382.2	99.6	0.521
	Placebo	250	2	0.8	0.1	2.9	-	-	-	-
≥14	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
≥15	HRV	498	1	0.2	0.0	1.1	49.8	-3840.6	99.4	1.000
	Placebo	250	1	0.4	0.0	2.2	-	-	-	-
≥16	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥17	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥18	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥19	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-
≥20	HRV	498	1	0.2	0.0	1.1	.	.	98.7	1.000
	Placebo	250	0	0.0	0.0	1.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 40 Efficacy of the vaccine against severe RV GE episodes leading to medical intervention with a score greater than or equal to X on the Vesikari scale from 2 weeks post Dose 2 to Visit 4 (ATP cohort for efficacy)



Supplement 41 Percentage of subjects reporting all cause GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 4 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	119	23.9	20.2	27.9	19.3	-9.4	40.1	0.172
Placebo	250	74	29.6	24.0	35.7	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 42 Percentage of subjects reporting all cause severe GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 4 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	14	2.8	1.5	4.7	29.7	-76.9	71.0	0.514
Placebo	250	10	4.0	1.9	7.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 43 Percentage of subjects hospitalised due to all cause GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks post Dose 2 up to Visit 4 - (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	498	7	1.4	0.6	2.9	-75.7	-1633.4	66.5	0.750
Placebo	250	2	0.8	0.1	2.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 44 Percentage of subjects who reported GE episodes, RV GE episodes, Severe RV GE episodes, and severe GE episodes leading to medical intervention from Visit 4 up to Visit 5 (ATP cohort for efficacy)

		HRV N = 487		Placebo N = 243		Total N = 730	
Characteristics	**Number of episodes**	**n**	**%**	**n**	**%**	**n**	**%**
GE	1	110	22.6	52	21.4	162	22.2
	2	10	2.1	9	3.7	19	2.6
	3	5	1.0	1	0.4	6	0.8
	4	2	0.4	0	0.0	2	0.3
	5	1	0.2	1	0.4	2	0.3
	Any	128	26.3	63	25.9	191	26.2
RV GE	1	9	1.8	22	9.1	31	4.2
	Any	9	1.8	22	9.1	31	4.2
Severe GE	1	23	4.7	17	7.0	40	5.5
	2	0	0.0	1	0.4	1	0.1
	Any	23	4.7	18	7.4	41	5.6
Severe RV GE	1	1	0.2	8	3.3	9	1.2
	Any	1	0.2	8	3.3	9	1.2

HRV = HRV group
Placebo = Placebo group
N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified number of episode

Supplement 45 Percentage of GE episodes leading to medical intervention with no available stool results from Visit 4 up to Visit 5 (ATP cohort for efficacy)

Category	HRV N'=158		Placebo N'=78	
	n	**%**	**n**	**%**
No stool results available	10	6.3	2	2.6
no stools collected	4	2.5	0	0.0
stools collected but no results available	6	3.8	2	2.6

HRV = HRV group
Placebo = Placebo group
N = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category
Any = number (percentage) of subjects reporting at least one specified symptom

Supplement 46 Number of GE episode and RV GE episodes leading to medical intervention reported from Visit 4 up to Visit 5 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

		HRV		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%
GE	Mild (1-6)	86	54.4	39	50.0
	Moderate (7-10)	49	31.0	20	25.6
	Severe (≥11)	23	14.6	19	24.4
	Any	158	100	78	100
RV GE	Mild (1-6)	3	33.3	6	27.3
	Moderate (7-10)	5	55.6	8	36.4
	Severe (≥11)	1	11.1	8	36.4
	Any	9	100	22	100

HRV = HRV group
Placebo = Placebo group
n (%) = Number (percentage) of specified events reported in each group, by severity using the 20 point vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of vesikari severity scale, in the considered efficacy follow-up period

Supplement 47 Percentage of subjects with RV GE episodes leading to medical intervention reported from Visit 4 up to Visit 5, by G type and P type (ATP cohort for efficacy)

	HRV N = 487		Placebo N = 243		Total N = 730	
Characteristics	n	%	n	%	n	%
Any	9	1.8	22	9.1	31	4.2
G1WT	4	0.8	13	5.3	17	2.3
G2	1	0.2	1	0.4	2	0.3
G3	2	0.4	7	2.9	9	1.2
G9	2	0.4	1	0.4	3	0.4
P4	1	0.2	1	0.4	2	0.3
P8 wild type	8	1.6	21	8.6	29	4.0

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 48 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from Visit 4 up to Visit 5, by G type and P type (ATP cohort for efficacy)

	HRV N = 487		Placebo N = 243		Total N = 730	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Any	1	0.2	8	3.3	9	1.2
G1WT	1	0.2	6	2.5	7	1.0
G3	0	0.0	2	0.8	2	0.3
P8 wild type	1	0.2	8	3.3	9	1.2

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 49 Number of RV GE episodes leading to medical intervention reported from Visit 4 up to Visit 5, by G and P type (ATP cohort for efficacy)

Type	HRV		Placebo	
	n	**%**	**n**	**%**
Any	9	100.0	22	100.0
G1WT+P8WT	4	44.44	13	59.09
G2+P4	1	11.11	1	4.55
G3+P8WT	2	22.22	7	31.82
G9+P8WT	2	22.22	1	4.55

HRV = HRV group
Placebo = Placebo group
n (%) = number (percentage) of RV GE episodes reporting the specified RV type in each group, among all RV GE episodes reported from visit 4 up to visit 5
Any = any specified symptom reported, regardless of the RV type

Supplement 50 Number of severe RV GE episodes leading to medical intervention reported from Visit 4 up to Visit 5, by G and P type (ATP cohort for efficacy)

Type	HRV		Placebo	
	n	**%**	**n**	**%**
Any	1	100.0	8	100.0
G1WT+P8WT	1	100.0	6	75.00
G3+P8WT	0	0.00	2	25.00

HRV = HRV group
Placebo = Placebo group
n (%) = number (percentage) of severe RV GE episodes reporting the specified RV type in each group, among all severe RV GE episodes reported from visit 4 up to visit 5
Any = any specified symptom reported, regardless of the RV type

Supplement 51 Duration (in years) of efficacy follow-up period from Visit 4 up to Visit 5 (ATP cohort for efficacy)

		HRV N = 487	Placebo N = 243
Characteristics	**Parameters**	**Value**	**Value**
Duration in years	Total	461.94	231.89
	Mean	0.95	0.95
	Minimum	0.13	0.21
	Q1	0.94	0.94
	Median	0.96	0.96
	Q3	0.97	0.98
	Maximum	1.03	1.07

HRV = HRV group
Placebo = Placebo group
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

Supplement 52 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	487	9	1.8	0.8	3.5	79.6	53.9	91.7	<0.001
Placebo	243	22	9.1	5.8	13.4	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 53 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 – by type (ATP cohort for efficacy)

				n/N			VE			
Type	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
G1WT	HRV	487	4	0.8	0.2	2.1	84.6	50.3	96.4	<0.001
	Placebo	243	13	5.3	2.9	9.0	-	-	-	-
G2	HRV	487	1	0.2	0.0	1.1	50.1	-3816.8	99.4	1.000
	Placebo	243	1	0.4	0.0	2.3	-	-	-	-
G3	HRV	487	2	0.4	0.0	1.5	85.7	25.1	98.6	0.016
	Placebo	243	7	2.9	1.2	5.8	-	-	-	-
G9	HRV	487	2	0.4	0.0	1.5	0.2	-5787.6	94.8	1.000
	Placebo	243	1	0.4	0.0	2.3	-	-	-	-
P8WT	HRV	487	8	1.6	0.7	3.2	81.0	55.3	92.7	<0.001
	Placebo	243	21	8.6	5.4	12.9	-	-	-	-
P4	HRV	487	1	0.2	0.0	1.1	50.1	-3816.8	99.4	1.000
	Placebo	243	1	0.4	0.0	2.3	-	-	-	-
Pooled	HRV	487	5	1.0	0.3	2.4	72.3	7.9	92.7	0.035
Non-G1	Placebo	243	9	3.7	1.7	6.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 54 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	487	1	0.2	0.0	1.1	93.8	53.5	99.9	0.002
Placebo	243	8	3.3	1.4	6.4	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 55 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 – by type (ATP cohort for efficacy)

				n/N			VE			
Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV	487	1	0.2	0.0	1.1	91.7	31.5	99.8	0.014
	Placebo	243	6	2.5	0.9	5.3	-	-	-	-
G3	HRV	487	0	0.0	0.0	0.8	100.0	-165.7	100.0	0.222
	Placebo	243	2	0.8	0.1	2.9	-	-	-	-
P8WT	HRV	487	1	0.2	0.0	1.1	93.8	53.5	99.9	0.002
	Placebo	243	8	3.3	1.4	6.4	-	-	-	-
Pooled	HRV	487	0	0.0	0.0	0.8	100.0	-165.7	100.0	0.222
Non-G1	Placebo	243	2	0.8	0.1	2.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 56 Percentage of subjects hospitalised due to RV GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 - (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	487	0	0.0	0.0	0.8	100.0	-1846.0	100.0	0.666
Placebo	243	1	0.4	0.0	2.3	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 57 Percentage of subjects reporting all cause GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	487	128	26.3	22.4	30.4	-1.4	-39.3	25.6	0.997
Placebo	243	63	25.9	20.5	31.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 58 Percentage of subjects reporting all cause severe GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	487	23	4.7	3.0	7.0	36.2	-25.4	67.1	0.205
Placebo	243	18	7.4	4.4	11.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 59 Percentage of subjects hospitalised due to all cause GE episodes leading to medical intervention and efficacy of the vaccine from Visit 4 up to Visit 5 (ATP cohort for efficacy)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	487	9	1.8	0.8	3.5	-12.3	-398.9	68.7	1.000
Placebo	243	4	1.6	0.5	4.2	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 60 Percentage of subjects reporting severe RV GE episodes leading to medical intervention with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Visit 4 up to Visit 5 (ATP cohort for efficacy)

				n/N			VE			
Vesikari score	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
≥11	HRV	487	1	0.2	0.0	1.1	93.8	53.5	99.9	0.002
	Placebo	243	8	3.3	1.4	6.4	-	-	-	-
≥12	HRV	487	0	0.0	0.0	0.8	100.0	57.6	100.0	0.003
	Placebo	243	6	2.5	0.9	5.3	-	-	-	-
≥13	HRV	487	0	0.0	0.0	0.8	100.0	45.5	100.0	0.008
	Placebo	243	5	2.1	0.7	4.7	-	-	-	-
≥14	HRV	487	0	0.0	0.0	0.8	100.0	24.4	100.0	0.025
	Placebo	243	4	1.6	0.5	4.2	-	-	-	-
≥15	HRV	487	0	0.0	0.0	0.8	100.0	-1846.0	100.0	0.666
	Placebo	243	1	0.4	0.0	2.3	-	-	-	-
≥16	HRV	487	0	0.0	0.0	0.8	100.0	-1846.0	100.0	0.666
	Placebo	243	1	0.4	0.0	2.3	-	-	-	-
≥17	HRV	487	0	0.0	0.0	0.8	.	.	.	-
	Placebo	243	0	0.0	0.0	1.5	-	-	-	-
≥18	HRV	487	0	0.0	0.0	0.8	.	.	.	-
	Placebo	243	0	0.0	0.0	1.5	-	-	-	-
≥19	HRV	487	0	0.0	0.0	0.8	.	.	.	-
	Placebo	243	0	0.0	0.0	1.5	-	-	-	-
≥20	HRV	487	0	0.0	0.0	0.8	.	.	.	-
	Placebo	243	0	0.0	0.0	1.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 61 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from Visit 4 up to Visit 5 (ATP cohort for efficacy)

		HRV N' = 9		Placebo N' = 22	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	7.6	-	9.4	-
	SD	2.1	-	3.6	-
	Median	8.0	-	9.5	-
	Minimum	4.0	-	2.0	-
	Maximum	11.0	-	16.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	7	77.8	18	81.8
	5	1	11.1	4	18.2
	more than 5 days	1	11.1	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	1	11.1	5	22.7
	4 to 5	4	44.4	4	18.2
	more than 5	4	44.4	13	59.1
Duration of vomiting (days)	0 day	4	44.4	3	13.6
	1 day	4	44.4	11	50.0
	2 days	1	11.1	4	18.2
	more than 2 days	0	0.0	4	18.2
Max number of episodes of vomiting /day	0	4	44.4	3	13.6
	1	3	33.3	4	18.2
	2 to 4	1	11.1	9	40.9
	more than 4	1	11.1	6	27.3
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	4.5
	37.1 to 38.4°C	3	33.3	8	36.4
	38.5 to 38.9°C	4	44.4	2	9.1
	more than 38.9°C	2	22.2	11	50.0
Treatment	none	7	77.8	16	72.7
	rehydration	2	22.2	5	22.7
	hospitalization	0	0.0	1	4.5
Dehydration	none	8	88.9	20	90.9
	1 to 5%	1	11.1	0	0.0
	more than 5 %	0	0.0	2	9.1

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 62 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from Visit 4 up to Visit 5 – by G1WT type (ATP cohort for efficacy)

		HRV N' = 4		Placebo N' = 13	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	8.0	-	10.0	-
	SD	2.2	-	3.8	-
	Median	7.5	-	10.0	-
	Minimum	6.0	-	2.0	-
	Maximum	11.0	-	16.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	3	75.0	10	76.9
	5	1	25.0	3	23.1
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	4	30.8
	4 to 5	2	50.0	1	7.7
	more than 5	2	50.0	8	61.5
Duration of vomiting (days)	0 day	2	50.0	2	15.4
	1 day	2	50.0	5	38.5
	2 days	0	0.0	2	15.4
	more than 2 days	0	0.0	4	30.8
Max number of episodes of vomiting /day	0	2	50.0	2	15.4
	1	1	25.0	2	15.4
	2 to 4	1	25.0	5	38.5
	more than 4	0	0.0	4	30.8
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	1	7.7
	37.1 to 38.4°C	0	0.0	1	7.7
	38.5 to 38.9°C	3	75.0	2	15.4
	more than 38.9°C	1	25.0	9	69.2
Treatment	none	3	75.0	10	76.9
	rehydration	1	25.0	2	15.4
	hospitalization	0	0.0	1	7.7
Dehydration	none	3	75.0	12	92.3
	1 to 5%	1	25.0	0	0.0
	more than 5 %	0	0.0	1	7.7

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 63 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from Visit 4 up to Visit 5 – by G2 type (ATP cohort for efficacy)

		HRV N' = 1		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	9.0	-	7.0	-
	SD	0.0	-	0.0	-
	Median	9.0	-	7.0	-
	Minimum	9.0	-	7.0	-
	Maximum	9.0	-	7.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	0	0.0	1	100
	5	0	0.0	0	0.0
	more than 5 days	1	100	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	1	100	1	100
	more than 5	0	0.0	0	0.0
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	0	0.0	1	100
	2 days	1	100	0	0.0
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	1	100	0	0.0
	2 to 4	0	0.0	1	100
	more than 4	0	0.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	100	1	100
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	0	0.0	0	0.0
Treatment	none	1	100	1	100
	rehydration	0	0.0	0	0.0
	hospitalization	0	0.0	0	0.0
Dehydration	none	1	100	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 64 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from Visit 4 up to Visit 5– by G3 type (ATP cohort for efficacy)

		HRV N' = 2		Placebo N' = 7	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	5.0	-	9.1	-
	SD	1.4	-	3.4	-
	Median	5.0	-	9.0	-
	Minimum	4.0	-	5.0	-
	Maximum	6.0	-	14.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	2	100	6	85.7
	5	0	0.0	1	14.3
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	1	50.0	1	14.3
	4 to 5	1	50.0	1	14.3
	more than 5	0	0.0	5	71.4
Duration of vomiting (days)	0 day	2	100	1	14.3
	1 day	0	0.0	4	57.1
	2 days	0	0.0	2	28.6
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	2	100	1	14.3
	1	0	0.0	1	14.3
	2 to 4	0	0.0	3	42.9
	more than 4	0	0.0	2	28.6
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	50.0	5	71.4
	38.5 to 38.9°C	0	0.0	0	0.0
	more than 38.9°C	1	50.0	2	28.6
Treatment	none	1	50.0	4	57.1
	rehydration	1	50.0	3	42.9
	hospitalization	0	0.0	0	0.0
Dehydration	none	2	100	6	85.7
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	1	14.3

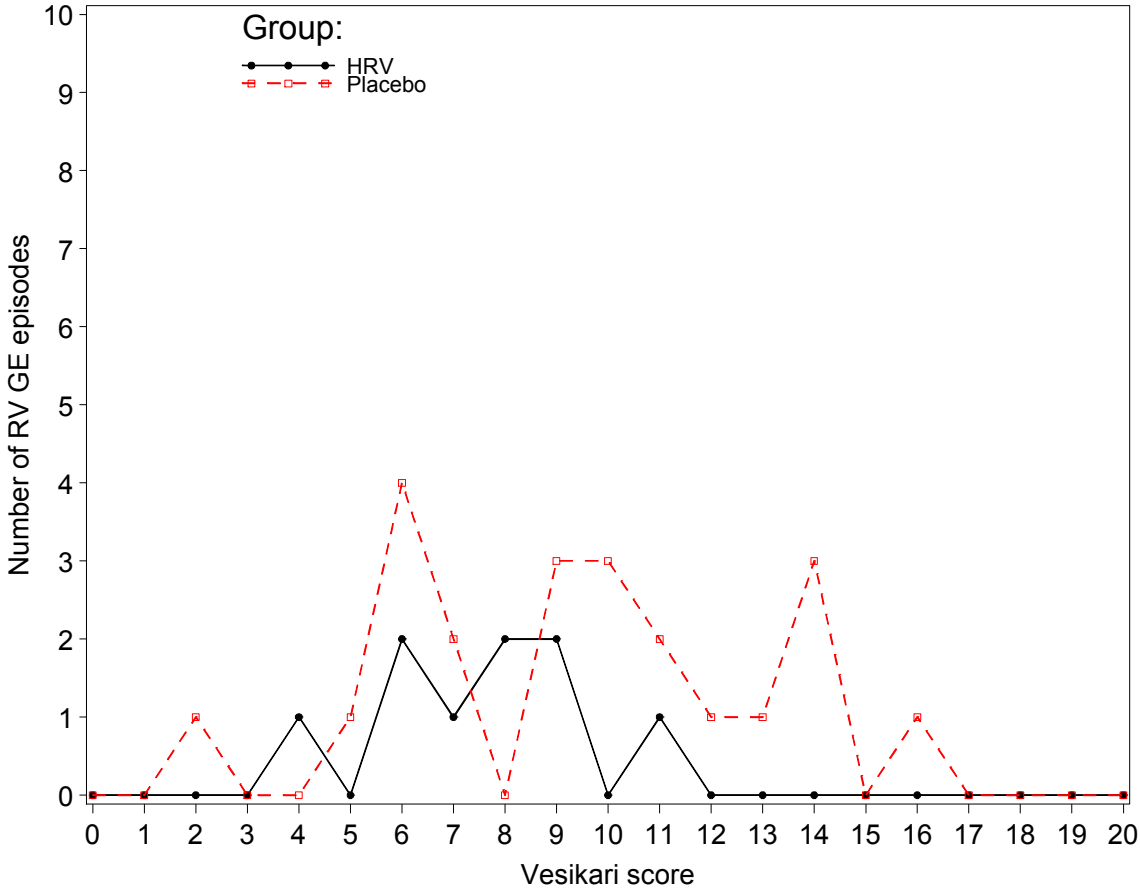
N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 65 Characteristics of the RV GE episodes leading to medical intervention (based on Vesikari scale) reported from Visit 4 up to Visit 5 – by G9 type (ATP cohort for efficacy)

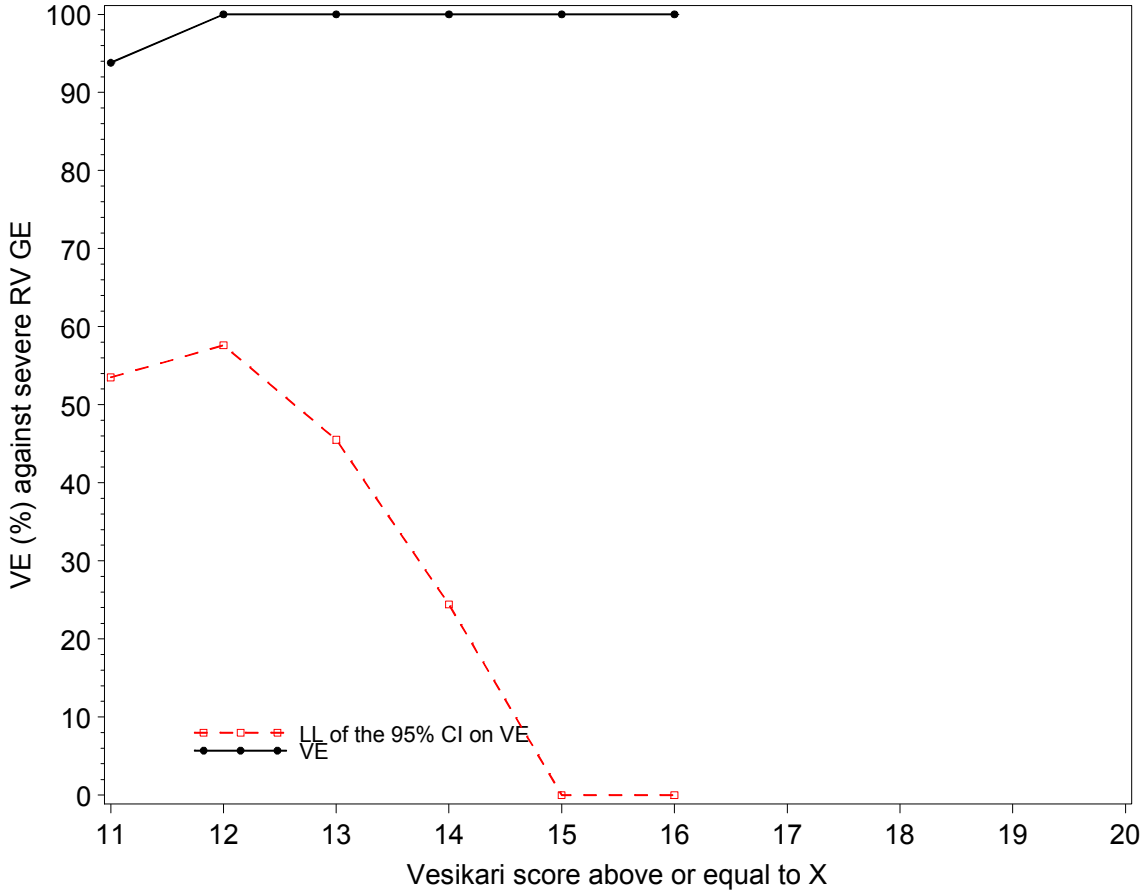
		HRV N' = 2		Placebo N' = 1	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Vesikari severity score	Mean	8.5	-	6.0	-
	SD	0.7	-	0.0	-
	Median	8.5	-	6.0	-
	Minimum	8.0	-	6.0	-
	Maximum	9.0	-	6.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1 to 4 days	2	100	1	100
	5	0	0.0	0	0.0
	more than 5 days	0	0.0	0	0.0
Maximum number of looser Than normal stools/day	0	0	0.0	0	0.0
	1 to 3	0	0.0	0	0.0
	4 to 5	0	0.0	1	100
	more than 5	2	100	0	0.0
Duration of vomiting (days)	0 day	0	0.0	0	0.0
	1 day	2	100	1	100
	2 days	0	0.0	0	0.0
	more than 2 days	0	0.0	0	0.0
Max number of episodes of vomiting /day	0	0	0.0	0	0.0
	1	1	50.0	1	100
	2 to 4	0	0.0	0	0.0
	more than 4	1	50.0	0	0.0
Maximum fever reported/day(rectal)	less than 37.1°C	0	0.0	0	0.0
	37.1 to 38.4°C	1	50.0	1	100
	38.5 to 38.9°C	1	50.0	0	0.0
	more than 38.9°C	0	0.0	0	0.0
Treatment	none	2	100	1	100
	rehydration	0	0.0	0	0.0
	hospitalization	0	0.0	0	0.0
Dehydration	none	2	100	1	100
	1 to 5%	0	0.0	0	0.0
	more than 5 %	0	0.0	0	0.0

N' = number of RV GE episodes reported in each group
n (%) = number (percentage) of specified symptom reported in each group among N
Value= value of the considered parameter
SD= standard deviation

Supplement 66 Distribution of Vesikari score for RV GE episodes leading to medical intervention reported from Visit 4 up to Visit 5 (ATP cohort for efficacy)



Supplement 67 Efficacy of the vaccine against severe RV GE episodes leading to medical intervention with a score greater than or equal to X on the Vesikari scale from Visit 4 up to Visit 5 (ATP cohort for efficacy)



Supplement 68 Percentage of subjects who reported GE episodes, RV GE episodes, Severe RV GE episodes, and severe GE episodes leading to medical intervention from Dose 1 to up to Visit 5 (Total vaccinated cohort)

		HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	**Number of episodes**	**n**	**%**	**n**	**%**	**n**	**%**
GE	1	141	27.8	77	30.0	218	28.5
	2	50	9.8	26	10.1	76	9.9
	3	14	2.8	15	5.8	29	3.8
	4	7	1.4	1	0.4	8	1.0
	5	3	0.6	0	0.0	3	0.4
	7	2	0.4	1	0.4	3	0.4
	Any	217	42.7	120	46.7	337	44.1
RV GE	1	14	2.8	36	14.0	50	6.5
	Any	14	2.8	36	14.0	50	6.5
Severe GE	1	35	6.9	23	8.9	58	7.6
	2	3	0.6	4	1.6	7	0.9
	Any	38	7.5	27	10.5	65	8.5
Severe RV GE	1	2	0.4	13	5.1	15	2.0
	Any	2	0.4	13	5.1	15	2.0

HRV = HRV group
Placebo = Placebo group
N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified number of episode
Any = number (percentage) of subjects reporting at least one specified symptom

Supplement 69 Percentage of GE episodes leading to medical intervention with no available stool results from Dose 1 up to Visit 5 (Total vaccinated cohort)

Category	HRV N'=340		Placebo N'=185	
	n	**%**	**n**	**%**
No stool results available	29	8.5	8	4.3
no stools collected	15	4.4	0	0.0
stools collected but no results available	14	4.1	8	4.3

HRV = HRV group
Placebo = Placebo group
N' = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 70 Number of GE episode and RV GE episodes leading to medical intervention reported from Dose 1 up to Visit 5 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

		HRV		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%
GE	Mild (1-6)	178	52.4	92	49.7
	Moderate (7-10)	121	35.6	62	33.5
	Severe (≥11)	41	12.1	31	16.8
	Any	340	100	185	100
RV GE	Mild (1-6)	6	42.9	10	27.8
	Moderate (7-10)	6	42.9	13	36.1
	Severe (≥11)	2	14.3	13	36.1
	Any	14	100	36	100

HRV = HRV group
Placebo = Placebo group
n (%) = Number (percentage) of specified events reported in each group, by severity using the 20 point Vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy follow-up period

Supplement 71 Percentage of subjects with RV GE episodes leading to medical intervention reported from Dose 1 up to Visit 5, by G type and P type (Total vaccinated cohort)

	HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	n	%	n	%	n	%
Any	14	2.8	36	14.0	50	6.5
G1WT	4	0.8	14	5.4	18	2.4
G2	1	0.2	2	0.8	3	0.4
G3	3	0.6	13	5.2	16	2.1
G4	1	0.2	1	0.4	2	0.3
G9	5	1.0	6	2.3	11	1.4
P4	1	0.2	2	0.8	3	0.4
P8 wild type	13	2.6	34	13.2	47	6.1

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 72 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from Dose 1 up to Visit 5, by G type and P type (Total vaccinated cohort)

	HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	**n**	**%**	**n**	**%**	**n**	**%**
Any	2	0.4	13	5.1	15	2.0
G1WT	1	0.2	6	2.3	7	0.9
G3	0	0.0	4	1.6	4	0.5
G9	1	0.2	3	1.2	4	0.5
P8 wild type	2	0.4	13	5.1	15	2.0

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 73 Duration (in years) of efficacy follow-up period from Dose 1 up to Visit 5 (Total vaccinated cohort)

		HRV N = 508	Placebo N = 257
Characteristics	**Parameters**	**Value**	**Value**
Duration in years	Total	911.33	458.33
	Mean	1.79	1.78
	Minimum	0.02	0.08
	Q1	1.82	1.82
	Median	1.85	1.85
	Q3	1.87	1.87
	Maximum	1.98	1.98

HRV = HRV group
Placebo = Placebo group
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

Supplement 74 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to Visit 5 (Total vaccinated cohort)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	508	14	2.8	1.5	4.6	80.3	62.6	90.2	<0.001
Placebo	257	36	14.0	10.0	18.9	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 75 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to Visit 5 – by type (Total vaccinated cohort)

			n/N			VE			
Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV	508	4	0.8	0.2	2.0	85.5	54.0	96.5	<0.001
	Placebo	257	14	5.4	3.0	9.0	-	-	-	-
G2	HRV	508	1	0.2	0.0	1.1	74.7	-385.9	99.6	0.526
	Placebo	257	2	0.8	0.1	2.8	-	-	-	-
G3	HRV	508	3	0.6	0.1	1.7	88.3	57.5	97.9	<0.001
	Placebo	257	13	5.1	2.7	8.5	-	-	-	-
G4	HRV	508	1	0.2	0.0	1.1	49.4	-3871.2	99.4	1.000
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
G9	HRV	508	5	1.0	0.3	2.3	57.8	-65.8	89.8	0.252
	Placebo	257	6	2.3	0.9	5.0	-	-	-	-
P8WT	HRV	508	13	2.6	1.4	4.3	80.7	62.4	90.6	<0.001
	Placebo	257	34	13.2	9.3	18.0	-	-	-	-
P4	HRV	508	1	0.2	0.0	1.1	74.7	-385.9	99.6	0.526
	Placebo	257	2	0.8	0.1	2.8	-	-	-	-
Pooled	HRV	508	10	2.0	0.9	3.6	77.0	49.4	90.3	<0.001
Non-G1	Placebo	257	22	8.6	5.4	12.7	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 76 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to Visit 5 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV	508	2	0.4	0.0	1.4	92.2	65.6	99.1	<0.001
Placebo	257	13	5.1	2.7	8.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 77 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to Visit 5 – by type (Total vaccinated cohort)

				n/N			VE			
Type	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
G1WT	HRV	508	1	0.2	0.0	1.1	91.6	30.5	99.8	0.014
	Placebo	257	6	2.3	0.9	5.0	-	-	-	-
G3	HRV	508	0	0.0	0.0	0.7	100.0	23.4	100.0	0.025
	Placebo	257	4	1.6	0.4	3.9	-	-	-	-
G9	HRV	508	1	0.2	0.0	1.1	83.1	-110.0	99.7	0.227
	Placebo	257	3	1.2	0.2	3.4	-	-	-	-
P8WT	HRV	508	2	0.4	0.0	1.4	92.2	65.6	99.1	<0.001
	Placebo	257	13	5.1	2.7	8.5	-	-	-	-
Pooled	HRV	508	1	0.2	0.0	1.1	92.8	43.7	99.8	0.005
Non-G1	Placebo	257	7	2.7	1.1	5.5	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 78 Percentage of subjects hospitalised due to RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to Visit 5 - (Total vaccinated cohort)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	508	1	0.2	0.0	1.1	74.7	-385.9	99.6	0.526
Placebo	257	2	0.8	0.1	2.8	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 79 Efficacy of the vaccine against any RV GE episodes leading to medical intervention from Dose 1 up to Visit 5 – by Cox method (Total vaccinated cohort)

				Person-year rate			VE			
Group	**N**	**n**	**T (year)**	**n/T**	**LL**	**UL**	**%**	**LL**	**UL**	**P-VALUE**
Any										
HRV	508	14	900.55	0.016	0.009	0.026	81.707	66.082	90.134	<0.001
Placebo	257	36	430.83	0.084	0.060	0.116	-	-	-	.
(G1WT)										
HRV	508	4	908.57	0.004	0.002	0.012	85.935	57.269	95.370	<0.001
Placebo	257	14	452.88	0.031	0.018	0.052	-	-	-	.
(Pooled Non-G1)										
HRV	508	10	901.91	0.011	0.006	0.021	78.103	53.758	89.631	<0.001
Placebo	257	22	435.58	0.051	0.033	0.077	-	-	-	.

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine efficacy (Cox regression model)
P-value from Cox regression model to test H0 = (VE=0%) (Y = Time to Event)

Supplement 80 Efficacy of the vaccine against severe RV GE episodes leading to medical intervention from Dose 1 up to Visit 5 - by Cox method (Total vaccinated cohort)

				Person-year rate			VE			
Group	**N**	**n**	**T (year)**	**n/T**	**LL**	**UL**	**%**	**LL**	**UL**	**P-VALUE**
Any										
HRV	508	2	908.47	0.002	0.001	0.009	92.454	66.562	98.297	<0.001
Placebo	257	13	447.71	0.029	0.017	0.050	-	-	-	.
(G1WT)										
HRV	508	1	909.74	0.001	0.000	0.008	91.694	31.013	99.000	0.021
Placebo	257	6	455.49	0.013	0.006	0.029	-	-	-	.
(Pooled Non-G1)										
HRV	508	1	908.67	0.001	0.000	0.008	92.922	42.475	99.129	0.013
Placebo	257	7	449.85	0.016	0.007	0.033	-	-	-	.

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group (without missing values)
n = number of subjects reporting at least one event(s) in each group
T (year) = sum of follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine efficacy (Cox regression model)
P-value from Cox regression model to test H0 = (VE=0%) (Y = Time to Event)

Supplement 81 Percentage of subjects who reported GE episodes, RV GE episodes, Severe RV GE episodes, and severe GE episodes leading to medical intervention from Dose 1 up to 2 weeks post Dose 2 (Total vaccinated cohort)

		HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	**Number of episodes**	**n**	**%**	**n**	**%**	**n**	**%**
GE	1	38	7.5	19	7.4	57	7.5
	2	3	0.6	0	0.0	3	0.4
	3	0	0.0	1	0.4	1	0.1
	Any	41	8.1	20	7.8	61	8.0
RV GE	1	0	0.0	2	0.8	2	0.3
	Any	0	0.0	2	0.8	2	0.3
Severe GE	1	3	0.6	1	0.4	4	0.5
	Any	3	0.6	1	0.4	4	0.5
Severe RV GE	1	0	0.0	1	0.4	1	0.1
	Any	0	0.0	1	0.4	1	0.1

HRV = HRV group
Placebo = Placebo group
N= Number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting the specified number of episode
Any = number (percentage) of subjects reporting at least one specified symptom

Supplement 82 Percentage of GE episodes leading to medical intervention with no available stool results from Dose 1 up to 2 weeks post Dose 2 (Total vaccinated cohort)

Category	HRV N'=44		Placebo N'=22	
	n	**%**	**n**	**%**
No stool results available	23	52.3	9	40.9
no stools collected	20	45.5	7	31.8
stools collected but no results available	3	6.8	2	9.1

HRV = HRV group
Placebo = Placebo group
N' = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 83 Number of GE episode and RV GE episodes leading to medical intervention reported from Dose 1 up to 2 weeks post Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

		HRV		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%
GE	Mild (1-6)	31	70.5	17	77.3
	Moderate (7-10)	10	22.7	4	18.2
	Severe (≥11)	3	6.8	1	4.5
	Any	44	100	22	100
RV GE	Mild (1-6)	0	0.0	0	0.0
	Moderate (7-10)	0	0.0	1	50.0
	Severe (≥11)	0	0.0	1	50.0
	Any	0	0.0	2	100

HRV = HRV group
Placebo = Placebo group
n (%) = Number (percentage) of specified events reported in each group, by severity using the 20 point Vesikari scale, among all specified events reported during the considered efficacy follow-up period
Any = any specified symptom reported, regardless of Vesikari severity scale, in the considered efficacy follow-up period

Supplement 84 Percentage of subjects with RV GE episodes leading to medical intervention reported from Dose 1 up to 2 weeks post Dose 2, by G type and P type (Total vaccinated cohort)

	HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	n	%	n	%	n	%
Any	0	0.0	2	0.8	2	0.3
G1WT	0	0.0	1	0.4	1	0.1
G9	0	0.0	1	0.4	1	0.1
P8 wild type	0	0.0	2	0.8	2	0.3

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the type

Supplement 85 Percentage of subjects with severe RV GE episodes leading to medical intervention reported from Dose 1 up to 2 weeks post Dose 2, by G type and P type (Total vaccinated cohort)

	HRV N = 508		Placebo N = 257		Total N = 765	
Characteristics	n	%	n	%	n	%
Any	0	0.0	1	0.4	1	0.1
G9	0	0.0	1	0.4	1	0.1
P8 wild type	0	0.0	1	0.4	1	0.1

HRV = HRV group
Placebo = Placebo group
N = number of subjects in each group for the considered efficacy follow-up period
n (%) = Number (percentage) of subjects reporting at least one specified RV type in each group
Any = number of subjects reporting at least one rotavirus gastroenteritis episodes, whatever is the RV type

Supplement 86 Duration (in years) of efficacy follow-up period from Dose 1 up to 2 weeks post Dose 2 (Total vaccinated cohort)

		HRV N = 508	Placebo N = 257
Characteristics	**Parameters**	**Value**	**Value**
Duration in years	Total	72.48	37.94
	Mean	0.14	0.15
	Minimum	0.02	0.08
	Q1	0.13	0.13
	Median	0.14	0.14
	Q3	0.14	0.14
	Maximum	0.88	0.91

HRV = HRV group
Placebo = Placebo group
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

Supplement 87 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to 2 weeks post Dose 2 (Total vaccinated cohort)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	508	0	0.0	0.0	0.7	100.0	-169.4	100.0	0.226
Placebo	257	2	0.8	0.1	2.8	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 88 Percentage of subjects reporting any RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to 2 weeks post Dose 2 – by type (Total vaccinated cohort)

				n/N			VE			
Type	**Group**	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
G1WT	HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
G9	HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
P8WT	HRV	508	0	0.0	0.0	0.7	100.0	-169.4	100.0	0.226
	Placebo	257	2	0.8	0.1	2.8	-	-	-	-
Pooled	HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
Non-G1	Placebo	257	1	0.4	0.0	2.1	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 89 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to 2 weeks post Dose 2 (Total vaccinated cohort)

			n/N			VE			
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
Placebo	257	1	0.4	0.0	2.1	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 90 Percentage of subjects reporting severe RV GE episodes leading to medical intervention and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 5 – by type (Total vaccinated cohort)

				n/N			VE			
Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G9	HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
P8WT	HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
	Placebo	257	1	0.4	0.0	2.1	-	-	-	-
Pooled	HRV	508	0	0.0	0.0	0.7	100.0	-1873.0	100.0	0.672
Non-G1	Placebo	257	1	0.4	0.0	2.1	-	-	-	-

HRV = HRV group
Placebo = Placebo group
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

Supplement 91 Percentage of subjects hospitalised due to RV GE episodes leading to medical intervention and efficacy of the vaccine from Dose 1 up to 2 weeks post Dose 2 - (Total vaccinated cohort)

No record exists for this table.

Supplement 92 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HRV N = 1007				Placebo N = 507			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		354	35.2	32.2	38.2	181	35.7	31.5	40.0
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Congenital, familial and genetic disorders (10010331)	Atrial septal defect (10003664)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Hydrocele (10020488)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Ear and labyrinth disorders (10013993)	Ear pain (10014020)	2	0.2	0.0	0.7	0	0.0	0.0	0.7
	Ear pruritus (10052138)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Otorrhoea (10033101)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
Eye disorders (10015919)	Conjunctivitis (10010741)	19	1.9	1.1	2.9	5	1.0	0.3	2.3
	Eye discharge (10015915)	11	1.1	0.5	1.9	6	1.2	0.4	2.6
	Ocular hyperaemia (10030041)	0	0.0	0.0	0.4	2	0.4	0.0	1.4
Gastrointestinal disorders (10017947)	Anal fissure (10002153)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
	Constipation (10010774)	16	1.6	0.9	2.6	11	2.2	1.1	3.8
	Diarrhoea (10012735)	4	0.4	0.1	1.0	2	0.4	0.0	1.4
	Epulis (10057974)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Flatulence (10016766)	0	0.0	0.0	0.4	2	0.4	0.0	1.4
	Gastrointestinal disorder (10017944)	4	0.4	0.1	1.0	4	0.8	0.2	2.0
	Haematochezia (10018836)	8	0.8	0.3	1.6	3	0.6	0.1	1.7
	Inguinal hernia (10022016)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Vomiting (10047700)	8	0.8	0.3	1.6	3	0.6	0.1	1.7
General disorders and administration site conditions (10018065)	Inflammation (10061218)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Irritability (10022998)	3	0.3	0.1	0.9	1	0.2	0.0	1.1
	Pyrexia (10037660)	5	0.5	0.2	1.2	7	1.4	0.6	2.8
Hepatobiliary disorders (10019805)	Hepatic failure (10019663)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Hepatic function abnormal (10019670)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Infections and infestations (10021881)	Adenovirus infection (10060931)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Bronchiolitis (10006448)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Bronchitis (10006451)	10	1.0	0.5	1.8	9	1.8	0.8	3.3

		HRV N = 1007				Placebo N = 507			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
	Candidiasis (10007152)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Eczema impetiginous (10051890)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Exanthema subitum (10015586)	5	0.5	0.2	1.2	0	0.0	0.0	0.7
	Fungal skin infection (10017543)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
	Gastroenteritis (10017888)	4	0.4	0.1	1.0	0	0.0	0.0	0.7
	Hand-foot-and-mouth disease (10019113)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Herpangina (10019936)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Hordeolum (10020377)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Impetigo (10021531)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
	Influenza (10022000)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
	Nasopharyngitis (10028810)	33	3.3	2.3	4.6	14	2.8	1.5	4.6
	Omphalitis (10030306)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
	Oral candidiasis (10030963)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
	Otitis externa (10033072)	2	0.2	0.0	0.7	0	0.0	0.0	0.7
	Otitis media (10033078)	1	0.1	0.0	0.6	2	0.4	0.0	1.4
	Pertussis (10034738)	0	0.0	0.0	0.4	2	0.4	0.0	1.4
	Pharyngitis (10034835)	2	0.2	0.0	0.7	0	0.0	0.0	0.7
	Pneumonia (10035664)	2	0.2	0.0	0.7	0	0.0	0.0	0.7
	Respiratory syncytial virus bronchiolitis (10038718)	4	0.4	0.1	1.0	1	0.2	0.0	1.1
	Respiratory syncytial virus infection (10061603)	6	0.6	0.2	1.3	1	0.2	0.0	1.1
	Rhinitis (10039083)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
	Trichophytosis (10067409)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Upper respiratory tract infection (10046306)	53	5.3	4.0	6.8	29	5.7	3.9	8.1
	Urinary tract infection (10046571)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Varicella (10046980)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
Injury, poisoning and procedural complications (10022117)	Arthropod bite (10003399)	3	0.3	0.1	0.9	3	0.6	0.1	1.7
	Arthropod sting (10003402)	0	0.0	0.0	0.4	1	0.2	0.0	1.1

		HRV N = 1007				Placebo N = 507			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
	Contusion (10050584)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Extradural haematoma (10015769)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Thermal burn (10053615)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Metabolism and nutrition disorders (10027433)	Weight gain poor (10047897)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Musculoskeletal and connective tissue disorders (10028395)	Muscular weakness (10028372)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Musculoskeletal chest pain (10050819)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Musculoskeletal pain (10028391)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Somnolence (10041349)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
Psychiatric disorders (10037175)	Nightmare (10029412)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
	Cough (10011224)	13	1.3	0.7	2.2	11	2.2	1.1	3.8
	Dysphonia (10013952)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Epistaxis (10015090)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Nasal congestion (10028735)	7	0.7	0.3	1.4	3	0.6	0.1	1.7
	Rhinorrhoea (10039101)	20	2.0	1.2	3.1	22	4.3	2.7	6.5
	Sneezing (10041232)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Upper airway obstruction (10067775)	4	0.4	0.1	1.0	2	0.4	0.0	1.4
	Upper respiratory tract inflammation (10049590)	38	3.8	2.7	5.1	20	3.9	2.4	6.0
Skin and subcutaneous tissue disorders (10040785)	Acne (10000496)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Asteatosis (10058130)	5	0.5	0.2	1.2	2	0.4	0.0	1.4
	Dermatitis (10012431)	0	0.0	0.0	0.4	3	0.6	0.1	1.7
	Dermatitis atopic (10012438)	2	0.2	0.0	0.7	1	0.2	0.0	1.1
	Dermatitis contact (10012442)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
	Dermatitis diaper (10012444)	16	1.6	0.9	2.6	11	2.2	1.1	3.8
	Dry skin (10013786)	12	1.2	0.6	2.1	5	1.0	0.3	2.3
	Eczema (10014184)	76	7.5	6.0	9.4	31	6.1	4.2	8.6

		HRV N = 1007				Placebo N = 507			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
	Eczema asteatotic (10014190)	0	0.0	0.0	0.4	2	0.4	0.0	1.4
	Eczema infantile (10014198)	11	1.1	0.5	1.9	3	0.6	0.1	1.7
	Heat rash (10019343)	18	1.8	1.1	2.8	0	0.0	0.0	0.7
	Intertrigo (10022622)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Pruritus (10037087)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Rash (10037844)	7	0.7	0.3	1.4	3	0.6	0.1	1.7
	Rash vesicular (10037898)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Seborrhoeic dermatitis (10039793)	7	0.7	0.3	1.4	2	0.4	0.0	1.4
	Urticaria (10046735)	3	0.3	0.1	0.9	1	0.2	0.0	1.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of administered doses
n (%) = number/percentage of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 93 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HRV N = 1007				Placebo N = 507			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		7	0.7	0.3	1.4	2	0.4	0.0	1.4
Gastrointestinal disorders (10017947)	Constipation (10010774)	0	0.0	0.0	0.4	2	0.4	0.0	1.4
	Gastrointestinal disorder (10017944)	3	0.3	0.1	0.9	0	0.0	0.0	0.7
	Haematochezia (10018836)	3	0.3	0.1	0.9	0	0.0	0.0	0.7
	Vomiting (10047700)	1	0.1	0.0	0.6	0	0.0	0.0	0.7

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of administered doses
n (%) = number (percentage) of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 94 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

		HRV N = 1007				Placebo N = 507			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		14	1.4	0.8	2.3	9	1.8	0.8	3.3
Gastrointestinal disorders (10017947)	Inguinal hernia (10022016)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Vomiting (10047700)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
Hepatobiliary disorders (10019805)	Hepatic failure (10019663)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
Infections and infestations (10021881)	Bronchitis (10006451)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
	Eczema impetiginous (10051890)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Gastroenteritis (10017888)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Influenza (10022000)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Nasopharyngitis (10028810)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Pneumonia (10035664)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Respiratory syncytial virus bronchiolitis (10038718)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Upper respiratory tract infection (10046306)	2	0.2	0.0	0.7	3	0.6	0.1	1.7
	Urinary tract infection (10046571)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	0	0.0	0.0	0.4	1	0.2	0.0	1.1
	Upper respiratory tract inflammation (10049590)	1	0.1	0.0	0.6	1	0.2	0.0	1.1
Skin and subcutaneous tissue disorders (10040785)	Dermatitis diaper (10012444)	1	0.1	0.0	0.6	0	0.0	0.0	0.7
	Eczema (10014184)	1	0.1	0.0	0.6	1	0.2	0.0	1.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of administered doses
n (%) = number (percentage) of doses with the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 95 Listing of SAEs (Total vaccinated cohort)

Group	Sub. No.	Case Id	Age at onset (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Intensity	Causality	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 96 Percentage of subjects with AEs leading to drop out classified by MedDRA Primary System Organ Class and Preferred Term during the study period (Total vaccinated cohort)

		HRV N = 508				Placebo N = 257			
				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom		1	0.2	0.0	1.1	1	0.4	0.0	2.1
Hepatobiliary disorders (10019805)	Hepatic failure (10019663)	1	0.2	0.0	1.1	0	0.0	0.0	1.4
Immune system disorders (10021428)	Anaphylactic reaction (10002198)	0	0.0	0.0	0.7	1	0.4	0.0	2.1

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n (%) = number (percentage) of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

11. REFERENCES

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12. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Director, Rotavirus vaccines
Global Clinical Research and Development

13.2. CIOMS

Sponsor Information

Sponsor Information Sheet

eTrack study number(s) and Abbreviated Title(s)	107625 (Rota-056)
Date of document	09 October 2009
Version of document	Version 1
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

1. Country

Japan

2. Co-ordinating Investigator/ Leiter der Klinishen Prüfung / Principal Investigators

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Not applicable

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(Study Contact for Emergency Code Break)
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Fax: [redacted] or [redacted]
Mobile phones for 7/7 day availability:
[redacted] (Head Safety Evaluation and Risk Management Pediatric)
Back-up mobile phone contact:
[redacted]

7. Study Centres

This study was conducted at 20 centres in Japan.

Protocol and Protocol Amendments

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107625 (Rota-056)
Amendment 1

Sponsor:
GSK Building
6-15, Sendagaya 4-chome
Shibuya-ku, Tokyo 151-8566
Japan

Study vaccine number	444563
Study vaccine	Lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	107625 (Rota-056)
Date of approval	Final: 30 March 2007
Amendment 1	Final: 07 May 2007
Title	Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Rotavirus Vaccine • [redacted] Central Study Co-ordinator • [redacted] Central Study Co-ordinator • [redacted] Statistician • [redacted] Manager, Clinical Development
Sponsor signatory:	[redacted] Director, Worldwide Clinical Development, Rotavirus vaccine, GSK Biologicals. [redacted] Deputy Director, Clinical Development, GlaxoSmithKline K.K.

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Synopsis

Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Indication/Study population	Primary immunisation of healthy infants against rotavirus disease/illness.
Rationale	GSK Biologicals' rotavirus vaccine is a live attenuated vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. The formulation consisting of a lyophilised HRV vaccine to be reconstituted with a suspension of calcium carbonate has been tested extensively in Phase I, II and III trials in a global development program and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants. This registration study is undertaken to provide the Regulatory Authorities in Japan with immunogenicity, efficacy, safety and reactogenicity data for the lyophilised formulation of GSK Biologicals' HRV vaccine when used in Japanese infants aged approximately 2 months at the time of the first dose. There will be an efficacy follow-up up to the time the infants are approximately two years of age.
Objectives	**Primary** • To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period. **Secondary** **Efficacy** • To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period. • To assess the efficacy of two doses of the lyophilised

formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.
- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity [in the immunogenicity subset (N = 60)]

- To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

Study design

- Experimental design: Phase III, randomised, double-blind, placebo-controlled, multicentre study in Japan with two parallel groups.
- Treatment allocation: Randomised (2:1 ratio).
- Blinding: Double-blind. Blinding will be maintained till the end of the study, i.e. Visit 5.

- Treatment Groups:
  - Group HRV lyophilised vaccine (N = 510)
  - Group Placebo (N = 255)
- Vaccination schedule: Vaccination according to 0, 1 month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks (42–104 days) at the time of the first dose.
- Control: Placebo.
- Routine childhood vaccination according to local practice can be administered concurrently with the study vaccinations as recommended in Japan. All vaccines administered from birth up to Visit 3 must be documented in the electronic case report form (eCRF).
- Eight day (Day 0 – Day 7) follow-up period for solicited symptoms (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) after any dose of HRV vaccine/Placebo using diary cards. Unsolicited symptoms will be followed up for a period of 31 days (Day 0 – Day 30).
- During the entire study period (from Dose 1 up to Visit 5 [two years of age]), active follow-up for occurrence of GE episodes (diarrhoea) leading to medical intervention via telephone contact or other means (at least every two weeks).
- For each GE episode leading to medical intervention occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after symptoms begin but preferably not later than 7 days after the onset of GE symptoms.
- Recording of SAEs throughout the study period.
- Blood samples (1 ml of whole blood to provide 0.4 ml of serum) will be drawn from subjects in the immunogenicity subset (N = 60) at Day 0 (i.e. Visit 1) and one month post Dose 2 (Month 2 i.e. Visit 3) to measure anti-rotavirus IgA antibody concentrations.
- Type of study: Self-contained.
- Data collection: Remote Data Entry (RDE).
- Five scheduled visits per subject: at Months 0, 1, 2 and

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one and two years of age.

- Duration of the study: The intended duration of the study, per subject will be till the subject is two years of age.
- Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

Number of subjects Target enrolment will be 765 subjects (510 subjects in HRV lyophilised vaccine group and 255 subjects in Placebo Group).

Primary endpoint

- Occurrence of any RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- Occurrence of each type of solicited symptom within the 8-day solicited follow-up period (Day 0 to Day 7) after

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each dose of HRV vaccine/Placebo.

- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Immunogenicity (in the immunogenicity subset N = 60)

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 3.

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APPENDICES

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List of Abbreviations

AE	Adverse event
AR	Attack rate
ATP	According-to-protocol
$CCID_{50}$	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
CTN	Clinical trial notification
DMEM	Dulbecco's Modified Eagle Medium
DTPa	Combined diphtheria, tetanus- acellular cell pertussis
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
eTrack	GSK tracking tool
Ffu	Foci Forming Units
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric Mean Antibody Concentration
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
HRV	Human Rotavirus
IB	Investigator Brochure
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
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
PCR	Polymerase Chain Reaction
RDE	Remote Data Entry
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBIR	Internet Randomisation tool
SOP	Standard Operating Procedure
UNICEF	United Nations Children's Fund
VE	Vaccine Efficacy
WHO	World Health Organisation

Glossary of Terms

Adverse event (AE):	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. When the subject, 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. 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 the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Diarrhoea:	Passage of three or more looser than normal stools within a day.
Efficacy follow-up period:	Period starting from two weeks after Dose 2 of HRV vaccine or placebo and ending either when 28 RV GE cases leading to medical intervention and caused by the circulating wild-type RV strains is accumulated or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all

	subjects reach two years of age, a final report will be present efficacy/safety/immunogenicity data up to time 28 RV GE episodes is reached and an annex report will present the efficacy/safety data up to two years of age.
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).
Gastroenteritis:	Diarrhoea with or without vomiting.
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 intervention:	Defined as medical doctor visit, an emergency room visit or hospitalisation
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 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.
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.

Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection
RV GE for primary efficacy analysis:	An episode of any severity GE leading to a medical intervention occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected as soon as possible but preferably not later than 7 days after the start of the episode.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.
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:	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 number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Subject:	Term used throughout the protocol 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.
Treatment number:	A unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

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 randomisation or treatment allocation.
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. INTRODUCTION

Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) among children worldwide. Review of epidemiological data estimated that, world-wide, RV causes approximately 138 -140 million cases of diarrhoea annually accounting for 20% of outpatient or clinic visits for diarrhoea, 26% of hospitalisations for diarrhoea and an estimated 440,000 deaths in children under 5 years of age per year [Parashar, 2003]. New surveillance data suggest that previous data are an underestimate and the mortality rate is now estimated to be as high as 611,000 (range 454,000 –705,000) annual deaths world-wide [Parashar, 2006]. The majority of these deaths occur in Africa, Indian subcontinent and Latin America. In developed countries, RV infection rarely results in death but RV remains the most common cause of hospitalisation for GE in children and leads to major medical and societal costs.

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 oral live attenuated vaccines receiving the most attention.

To meet this health need, GlaxoSmithKline (GSK) Biologicals has developed an attenuated vaccine which is based on a human rotavirus (HRV) strain designated as RIX4414. The vaccine strain RIX4414 was derived from the parent 89-12 HRV strain belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old child with a mild RV diarrhoea in December 1988. A candidate vaccine based on the 89-12 HRV strain at passage 33 in African Green Monkey Kidney cells was shown to be safe, immunogenic and efficacious against RV GE over two consecutive RV seasons in infants [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002]. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilised HRV vaccine containing RIX4414, a cloned passage 43 derivative from 89-12, for oral administration after reconstitution with a separately supplied liquid calcium carbonate buffer.

1.1. Background

GSK Biologicals' HRV vaccine (Rotarix) is currently licensed in a total of 89 countries in Latin America, Asia, Middle-East, Africa and the European Union.

GSK Biologicals' HRV vaccine was tested in Phase I studies conducted in adults, previously infected children (1-3 years old), followed by Phase II and Phase III studies among infants in Asia, Africa, Europe, Latin America and North America. In all studies, the adverse reaction profile in infants receiving HRV vaccine was similar to infants receiving Placebo. A large safety trial conducted in Latin America and Finland where 63,225 subjects were enrolled gave evidence of no increased risk of intussusception (IS) in the HRV vaccine Group when compared with the Placebo Group. The HRV vaccine was highly efficacious in protecting infants against RV GE.

The protective efficacy of the HRV vaccine against any or severe RV GE, as well as against hospitalisation for RV GE was demonstrated in phase II studies in Finland [Vesikari, 2004] and Latin America (Brazil, Mexico and Venezuela) [Salinas, 2005].

In Finland (Study Rota-004) [Vesikari, 2004], two doses of HRV 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.

In Latin America (Brazil, Mexico and Venezuela) (Study Rota-006) [Salinas, 2005], the efficacy of the HRV vaccine in preventing RV GE was demonstrated in a setting with different circulating serotypes (G1 and non-G1 RV types). Two doses of the HRV vaccine at three virus concentrations ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu) were 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-HBV] and Hib). For the first year efficacy follow-up, the protective efficacy of the HRV vaccine (pooled HRV vaccine Groups) was 61.4% (95% CI: 42.3%; 74.1%) against any RV diarrhoea, 74.1% (95% CI: 55.8%; 85.0%) against severe RV diarrhoea (an episode with a score ≥ 11 on the 20-point Vesikari scale [Ruuska, 1990]) and 79.0% (95% CI: 48.0%; 92.0%) against hospitalised RV diarrhoea. The vaccine efficacy against severe RV GE was 74.7% (95% CI: 37.7%; 90.1%) over two consecutive efficacy follow-up periods.

A large phase III multinational trial (Rota-023) involving 63,225 infants was undertaken in 11 countries in Latin America and in Finland with a co-primary objective of assessing the safety of the HRV vaccine in terms of occurrence of definite IS [Ruiz-Palacios, 2006]. The primary safety evaluation was based on occurrence of definite IS during 31 days (Day 0 to Day 30) after each vaccine dose. 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. The overall SAE profile of the HRV vaccine was similar to the Placebo. The SAE profile appeared to be in favour of the HRV vaccine with respect to preventing GE-related SAEs.

Study Rota-023 is 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. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV strains during the period starting from completion of the immunisation (2 weeks post Dose 2) until one year of age was 84.7% (95% CI: 71.7%; 92.4%) (primary efficacy endpoint). 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%). A subset of children was followed up until 24 months of age. Vaccine efficacy against severe RV GE was 79.0% (95% CI: 66.4%; 87.4%) during the second year and 80.5% (95% CI: 71.3%; 87.1%) during the

entire two year follow-up. Efficacy against G1 and non-G1 RV types was consistent during each follow-up period. The results from this study confirm that this human attenuated G1P[8] HRV vaccine elicits cross-protection, and provide evidence that the HRV vaccine effectively protects vaccinated children against the commonly circulating RV types during the first two years of life. Among the subjects followed until one year of age and until two years of age, there was no increased risk of definite IS respectively diagnosed from Dose 1 up to one year of age and from Dose 1 up to two years of age in the HRV vaccine Group versus Placebo.

A phase III study conducted in six European countries (Rota-036) evaluated two doses of the HRV vaccine when co-administered with routine infant vaccinations: Infanrix Hexa (combined diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, inactivated polio and *Haemophilus influenzae* type b vaccine), Infanrix Polio Hib (combined diphtheria and tetanus toxoids, acellular pertussis, inactivated polio and *Haemophilus influenzae* type b vaccine), Prevnar (7-valent pneumococcal polysaccharide conjugate vaccine) and Meningitec (meningococcal group C conjugate vaccine). This study has confirmed the efficacy of HRV vaccine against RV GE hospitalisations, any and severe RV GE due to G1 and non-G1 RV and the important reduction of severe GE of any cause. The first efficacy follow-up period started from two weeks after Dose 2 and ended June –July 2005. A total of 3874 subjects were part of the 1st year according-to-protocol (ATP) cohort for efficacy. Vaccine efficacy was 87.1% (95% CI: 79.6%; 92.1%) against any episodes of RV GE and 95.8% (95% CI: 89.6%; 98.7%) against severe RV GE episodes. For increasing disease severity with Vesikari scores between 11 and 20, VE was increasingly higher, reaching 100% against more severe RV GE (Vesikari score ≥ 17 points). VE against hospitalisation for RV GE was 100% (95% CI: 81.8%; 100%) and against RV GE episodes requiring medical attention was 91.8% (95% CI: 84.0%; 96.3%). The HRV vaccine was significantly protective against any and severe RV GE caused by G1, G3, G4 and G9 RV strains. Protective trend was observed against G2 RV type that does not share any of the outer or inner capsid antigens of the HRV vaccine.

Study Rota-036 also provided key co-administration data by evaluating the co-administration of HRV vaccine with currently used childhood vaccinations given according to the primary vaccination schedules in each participating country. Co-administration of HRV vaccine with routinely used Infanrix Hexa, Infanrix Polio Hib, Prevnar 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 Geometric Mean antibody Concentration/Titre (GMCs/GMTs) for antibodies to diphtheria, tetanus, pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), hepatitis B surface antigen (HBs), poliovirus serotypes 1, 2 and 3, and polyribosyl ribitol phosphate (PRP) were similar between the HRV vaccine and Placebo Groups after three doses of childhood vaccinations. In France and Germany, Post Dose 3 response to each of the seven *Streptococcus pneumoniae* serotypes, 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.

Please refer to the latest edition of the Investigator Brochure (edition 7 or later) for a review of the pre-clinical and clinical studies of GSK Biologicals' HRV vaccine.

1.2. Rationale for the study

GSK Biologicals' rotavirus vaccine is a live attenuated vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. The formulation consisting of a lyophilised HRV vaccine to be reconstituted with a suspension of calcium carbonate has been tested extensively in Phase I, II and III trials in a global development program and found to be well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.

This registration study is being undertaken to provide the Regulatory Authorities in Japan with immunogenicity, efficacy, safety and reactogenicity data for the lyophilised formulation of GSK Biologicals' HRV vaccine when used in Japanese infants aged approximately 2 months at the time of the first dose. There will be an efficacy follow-up up to the time that the infants are approximately two years of age.

2. OBJECTIVES

2.1. Primary objective

- To determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

Efficacy

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.

- To assess the efficacy of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

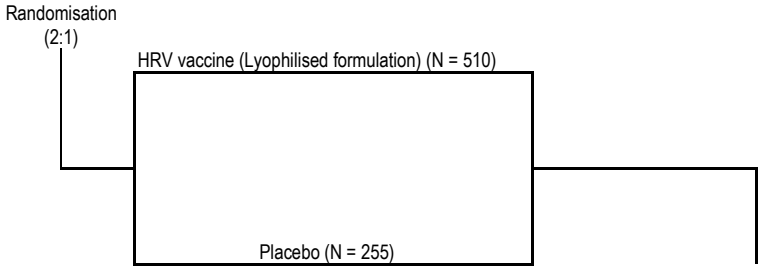
- To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.
- To assess the safety of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity [in the immunogenicity subset (N = 60)]

- To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

Refer to Section 10.2 for definitions of secondary endpoints.

3. STUDY DESIGN OVERVIEW



	Vaccination Visits			Safety and efficacy follow-up Visits	
	Visit 1	Visit 2	Visit 3	Visit 4#	Visit 5#
	Dose 1	Dose 2			
	Day 0	Month 1	Month 2		
Age:	6 – 14 weeks			1 year	2 years
	Blood sampling*		Blood sampling*		

N: Number of subjects planned to be enrolled.
HRV: Human rotavirus
*: Blood sampling in the immunogenicity subset (N = 60)
#: Safety and efficacy follow-up visits.

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- Experimental design: Phase III, randomised, double-blind, placebo-controlled, multicentre study in Japan with two parallel groups.
- Treatment allocation: Randomised (2:1 ratio).
- Blinding: Double-blind. Blinding will be maintained till the end of the study, i.e. Visit 5.
- Treatment Groups:
  - Group HRV lyophilised vaccine (N = 510)
  - Group Placebo (N = 255)
- Vaccination schedule: Vaccination according to 0, 1 month schedule against rotavirus diseases in healthy infants aged 6 to 14 weeks (42–104 days) at the time of the first dose.
- Control: Placebo.
- Routine childhood vaccination according to local practice can be administered concurrently with the study vaccinations as recommended in Japan. All vaccines administered from birth up to Visit 3 must be documented in the electronic case report form (eCRF).
- Eight day (Day 0 – Day 7) follow-up period for solicited symptoms (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) after any dose of HRV vaccine/Placebo using diary cards. Unsolicited symptoms will be followed up for a period of 31 days (Day 0 – Day 30).
- During the entire study period (from Dose 1 up to Visit 5 [two years of age]), active follow-up for occurrence of GE episodes (diarrhoea) leading to medical intervention via telephone contact or other means (at least every two weeks).
- For each GE episode leading to medical intervention occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after symptoms begin but preferably not later than 7 days after the onset of GE symptoms.
- Recording of SAEs throughout the study period.
- Blood samples (1 ml of whole blood to provide 0.4 ml of serum) will be drawn from subjects in the immunogenicity subset (N = 60) at Day 0 (i.e. Visit 1) and one month post Dose 2 (Month 2 i.e. Visit 3) to measure anti-rotavirus IgA antibody concentrations.
- Type of study: Self-contained.
- Data collection: Remote Data Entry (RDE).
- Five scheduled visits per subject: at Months 0, 1, 2 and one and two years of age.
- Duration of the study: The intended duration of the study, per subject will be till the subject is two years of age (refer to Appendix C for recruitment details).

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- Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

4. STUDY COHORT

4.1. Number of subjects/centres

Target enrolment will be 765 subjects (510 subjects in HRV lyophilised vaccine Group and 255 subjects in Placebo Group). All subjects will be enrolled at multiple sites in Japan.

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) should be enrolled in the study.
- A male or female infant 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/guardian of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born between a gestation period of 36 and 42 weeks inclusive.

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 within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- History of use of experimental rotavirus vaccine.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs prior to the first vaccine dose. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)

- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition determined by the investigator.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- A family history of congenital or hereditary immunodeficiency.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.
- 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. Axillary temperature <37.5°C.) Temperature greater than or equal to these cut-offs warrants deferral of the vaccination pending recovery of the subject.
- Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of RV GE.
- Concurrently participating in another clinical study, at any time during the study period in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

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 during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids are allowed).
- Administration of immunoglobulin 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

The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine/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 8.7):

- Known hypersensitivity after previous administration of HRV vaccine or to any component of the vaccine.
- Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following AEs constitute contraindications to administration of HRV vaccine/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).

- Acute severe febrile illness.
- Diarrhoea or vomiting.

5. STUDY CONDUCT CONSIDERATIONS

5.1. Ethics and regulatory considerations

5.1.1. Clinical Trial Notification (CTN) to Regulatory Authority

GSK Biologicals' will submit the clinical trial notification (CTN) to the regulatory authorities in accordance with Article 80-2 of the Pharmaceutical Affairs Law prior to a site initiating the study in Japan.

5.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with the Declaration of Helsinki [(South Africa, 1996), Appendix A], Articles 14-3 and 80-2 of the Pharmaceutical Affairs Law, Good Clinical Practice (GCP) (MHW Ordinance No.28, March 27, 1997) and Revised GCP (MHLW Ordinance No.106, June 12, 2003), while ensuring the protection of human subjects.

The scientific rationale for and ethical conduct of the study should be reviewed and approved by the Institutional Review Board (IRB). If the protocol, informed consent form, or any other information that the IRB has approved is amended during the study, the IRB must review and approve these amended documents. Any revised informed consent form and any other information should receive the IRB's approval in advance of use for the enrollment of new subjects.

The investigator and GSK should provide the head of the medical institution with the current protocol, informed consent form and other written information, Investigator Brochure (IB), and other documents to be reviewed by the IRB. The head of the medical institution will submit these documents to the IRB before he/she approves the conduct of the study.

After the IRB makes a decision on whether the study may be conducted or not and notifies it to the head of the medical institution, the head of the medical institution will give his/her instruction or notify his/her decision in writing based on the IRB's decision to the investigator and sponsor together with the IRB's dated document on its decision. If the IRB disapproves of the conduct of the study, the head of the medical institution must not approve it.

The investigator and the head of the medical institution agree to allow the IRB direct access to all relevant documents.

The IRB must be constituted in accordance with all applicable regulatory requirements.

5.1.3. Informed Consent of Subjects

Informed consent will be obtained from the parents/guardians of the subjects before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

While informed consent information can be presented to groups at an initial information session, parents/guardians of each subject must be given the opportunity to individually pose questions to the investigator or designate prior to the subject dating and signing the Informed Consent Form.

5.1.3.1. Informed Consent

Prior to the start of the study, the investigator/sub-investigator should fully inform the parents/guardians of potential subject of the study including the written information given approval by the IRB. The investigator/sub-investigator should provide the parents/guardians of subject ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. After giving informed consent based on his/her free will, the parents/guardians of the subject should sign and personally date the consent form. The person who conducted the informed consent discussion should sign and personally date the consent form. If the parents/guardians of the subject are unable to read, an impartial witness should be present during the entire informed consent discussion, and the witness should sign and personally date the consent form. The investigator/sub-investigator should retain this signed and dated form and other written information together with the source medical records, such as clinical charts (in accordance with the rules for records retention, if any, at each medical institution) and give a copy to the subject.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the parents/guardians of the subjects should include explanations of the following:

a. That the study involves research.

b. The purpose of the study.

c. The methods of the study (those aspects of the study that are experimental, inclusion criteria, the probability for random assignment to each treatment in a randomisation study).

d. The expected duration of the subject's participation in the study.

e. The approximate number of subjects involved in the study.

f. The reasonably foreseeable benefits and risks or inconveniences to the subject.

g. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

h. The compensation and/or treatment available to the subject in the event of study-related injury.

i. That the subject's participation in the study is voluntary and that the parents/guardians of the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

j. That the parents/guardians of the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

k. The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.

l. That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the parents/guardians of the subject is authorising such access.

m. If the results of the study are published, the subject's identity will remain confidential.

n. The anticipated expenses, if any, to the subject for participating in the study.

o. The anticipated prorated payment, if any, to the subject for participating in the study.

p. Name, title, and contact address of the investigator/sub-investigator.

q. The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.

r. The responsibilities of the subjects' parents/guardians.

5.1.3.2.Revision of informed consent form and other written information.

If information becomes available that may be relevant to the parents/guardians of the subject's willingness to continue participation in the study, the investigator/sub-investigator should immediately inform the parents/guardians of the subject of it to

confirm the willingness to continue participation in the study, and document the communication of this information (in medical records). If necessary, the investigator should revise the written information to be provided to the parents/guardians of the subjects, promptly report it to the sponsor, and obtain approval from the IRB. The investigator should not enroll any new subject in the study before the IRB's approval. After the IRB approves the revision of the written information to be provided to the parents/guardians of the subjects, the investigator/sub-investigator should inform the parents/guardians of each subject participating in the study of the revised written information, and obtain written informed consent.

5.1.4. Investigator Reporting Requirements

As indicated in section 8.9 (Regulatory Reporting Requirements for SAEs), the investigator is responsible for reporting all SAEs to the head of the medical institution. Furthermore, the investigator is responsible for reporting the summary status of the study in writing annually or more frequently if requested by the IRB to the head of the medical institution for continuing review by the IRB. The investigator is also responsible for notifying the head of the medical institution of the termination, suspension, or completion of the study.

5.2. General study aspects

5.2.1. Routine vaccinations

DTPa and HBV vaccines are allowed to be co-administered along with HRV vaccine/Placebo. Administration of all routine childhood vaccinations since birth up to Visit 3 must be documented in the eCRF.

5.2.2. Feeding

There are no restrictions on feeding, neither before nor after HRV vaccine/Placebo administration.

5.2.3. Surveillance of GE leading to medical intervention and collection of GE stool samples

Active follow-up for occurrence of GE leading to medical intervention will be conducted during the period starting from administration of Dose 1 up to the last visit planned for the subject. From Day 7 after Dose 1 of HRV vaccine or Placebo until end of study visit, the intention is to make contact with each subject's parent/guardian at least once every two weeks to check on the occurrence of any GE leading to medical intervention. This contact will be by telephone, short message service (SMS) using cellular phone, an Independent Calling Centre or health care workers or other convenient means. 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 leading to medical intervention 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 leading to medical intervention 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.

Parents/guardians should be instructed to collect stool sample(s) from the subject if the subject develops GE leading to medical intervention during the entire study period. Refer to the glossary of terms for definition of diarrhoea/GE. A stool sample should be collected as soon as possible after illness begins and preferably not later than 7 days after the start of the GE episode. A stool sample should be collected for each GE episode. A second stool sample should be collected if the first sample is insufficient. Two occurrences of GE should be classified as separate episodes, if there are 5 or more diarrhoea-free days between the episodes.

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 consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.4. Outline of study procedures

Table 1 presents the outline of study procedures.

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Table 1 List of study procedures

Age	6-14 weeks			One year	Two years
Visits Timing Sampling time point	VISIT 1 Day 0 Pre-vacc	VISIT 2 Month 1	VISIT 3 Month 2 Post-vacc 2	VISIT 4	VISIT 5
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	●	●	-	-	-
Randomisation	●	-	-	-	-
Blood sampling (1 ml) for antibody determination in an immunogenicity subset *	●	-	●	-	-
Study vaccination (HRV vaccine/ Placebo)	●	●	-	-	-
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians	●	●	-	-	-
Return of reactogenicity diary card	-	○	○	-	-
Transcription of the reactogenicity diary card		●	●	-	-
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●	-	-
Record any concomitant medication/vaccination, by investigator	●	●	●	●#	●#
Recording of GE leading to medical intervention occurring throughout the study period	●	●	●	●	●
Contact the subject's parent/gardian to check GE occurrence at least every two weeks	○	○	○	○	○
Collection of stool samples if subject has GE leading to medical intervention	●	●	●	●	●
Return of GE diary card	-	○	○	○	○
GE diary card transcription	-	●	●	●	●
Recording of SAEs	●	●	●	●	●
Reporting AEs leading to drop-out	●	●	●	●	●
Conclusion at Visit 4				●	
Study conclusion	-	-	-	-	●

Note: Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Blood sampling will be done only from subjects in the immunogenicity subset (N = 60).

for concomitant medication administered for the treatment of an AE leading to drop-out/SAE.

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It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed.

Table 2 Intervals between study visits

Interval /Visit	Range of interval /Visit
Visit 1→Visit 2	30 - 48 days
Visit 2→Visit 3	30 - 48 days
Visit 4	1 year of age ± 15 days
Visit 5	2 years of age ± 15 days

N.B: The reference date for intervals between study visits: the first vaccination date

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 clinical samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E .

The detailed description of procedures to be performed during each study visit is presented below:

Visit 1 (Day 0): Dose 1 of the HRV vaccine/Placebo (at 6 -14 weeks of age)

- Written informed consent obtained from the parents/guardians of the subject.
- Checking inclusion/exclusion criteria (refer to section 4.2 and 4.3).
- Checking of contraindications to vaccination (refer to section 4.5).
- Recording of medical history and physical examination.
- Recording of pre-vaccination body temperature (measured by an axillary thermometer).
- Measurement of height and weight.
- Recording of feeding practice.
- Random allocation of the subjects into one of the two study groups.
- Collection of blood sample from subjects in the immunogenicity subset (N = 60) for serology prior to vaccination: a minimum of 1 ml of whole blood will be withdrawn to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Vaccination:
  - Study vaccination: HRV vaccine/Placebo.

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 the HRV vaccine/placebo.

- Diary cards will be provided to the parents/guardians of all subjects to record information on solicited symptoms (fever, fussiness/irritability, loss of appetite cough/runny nose, diarrhoea and vomiting) occurring on the day of Dose 1 and the following 7 days, on any medications and unsolicited AE occurring within 31 days after Dose 1, as well as on any GE leading to medical intervention occurring until Visit 2. The parents/guardians should be instructed to return the completed diary card to the investigator at Visit 2.
- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- The subjects' parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 1 and 2. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- Recording of any prior/concomitant medication (including vaccinations) administered.
- Recording of SAEs.

Visit 2 (Month 1): Dose 2 of the HRV vaccine/Placebo

- Checking elimination criteria (refer section 4.4).
- Checking contraindications to vaccination (refer to section 4.5).
- Recording of concomitant medication/vaccination administered.
- Physical examination.
- Recording of pre-vaccination of body temperature (measured by axillary thermometers)
- Recording of feeding practice.
- Collection and verification of diary card containing information on solicited symptoms/medication/adverse events/GE leading to medical intervention occurring from Visit 1 till Visit 2. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.

- Vaccination:
  - Study vaccination: HRV vaccine/Placebo.

  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 the HRV vaccine/placebo.
- Diary cards will be provided to the parents/guardians of all subjects to record information on solicited symptoms (fever, fussiness/irritability, loss of appetite cough/runny nose, diarrhoea and vomiting) occurring on the day of Dose 2 and the following 7 days, on any medications and unsolicited AEs occurring within 31 days after Dose 2 as well as on any GE leading to medical intervention occurring until Visit 3. The parents/guardians should be instructed to return the completed diary card to the investigator at Visit 3.
- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- The subjects' parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 2 and 3. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording of SAEs.
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.

Visit 3 (Month 2): Follow-up visit

- Physical examination.
- Checking elimination criteria (refer section 4.4).
- Recording of any concomitant medication/vaccination administered.
- Collection of post-vaccination blood sample from subjects in the immunogenicity subset (N = 60): a minimum of 1 ml of whole blood will be withdrawn to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Collection and verification of diary card containing information on solicited symptoms/medication/adverse event/GE leading to medical intervention occurring from Visit 2 till Visit 3. The investigator will verify the diary card and transcribe the

information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.

- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 3 and 4. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- A "GE diary card" will be provided to parents/guardians of all subjects and will be used by the study staff during contact visits to record information on any GE episodes leading to medical intervention occurring until Visit 4. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording of SAEs.
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.
- All parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 4 (One year of age): Follow-up Visit

- Physical examination.
- Checking elimination criteria (refer section 4.4).
- Collection and verification of GE diary card containing information on GE leading to medical intervention occurring from Visit 3 till Visit 4. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.
- Parents/guardians of all subjects will be instructed to collect stool sample(s) from the subject if they suspect that the subject has GE (diarrhoea) leading to medical intervention between Visits 4 and 5. A stool sample should be collected as soon as possible and preferably not later than 7 days after the onset of GE. Two occurrences of GE symptoms should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes. Stool sample(s) should be collected for each separate GE episode. The study personnel may organise transportation of the stool samples.
- A "GE diary card" will be provided to parents/guardians of all subjects and will be used by the study staff during contact visits to record information on any GE episodes leading to medical intervention occurring until Visit 5. The

parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.

- Active follow-up (at least once every two weeks) for occurrence of GE episodes will be done by study staff (telephone contact or other means).
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording of any concomitant medication for the treatment of an AE leading to drop-out/SAE.
- Recording of SAEs.
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.
- All parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- Conclusion at Visit 4.

Visit 5 (Two years of age): Follow-up Visit

- Physical examination.
- Checking of elimination criteria.
- Collection and verification of GE diary card containing information on GE leading to medical intervention occurring from Visit 4 till Visit 5. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation.
- Recording of SAEs.
- Collection of any stool samples (in case of GE leading to medical intervention).
- Recording any AEs leading to drop-out that may have occurred since the previous visit in the eCRF.
- Recording of any concomitant medication for the treatment of an AE leading to drop-out/SAE.
- Study conclusion.

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

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.

GE stool analysis

Stool samples collected during each GE episode leading to medical intervention from Visit 1 until Visit 5 will be tested at GSK Biologicals or a laboratory designated by GSK Biologicals using ELISA to detect RV. If positive, the sample will be tested by polymerase chain reaction (PCR) to determine the G and the P genotypes. If any G1 RV is detected, vaccine virus will be differentiated from the wild type serotype by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) followed by reverse hybridisation assay or an equivalent approach (Refer Appendix F).

Serum analysis

Serum obtained from whole blood samples collected from subjects in the immunogenicity subset at Visit 1 and Visit 3 will be tested by ELISA at GSK Biologicals' central laboratory (or validated laboratory designated by GSK Biologicals) to measure serum anti-rotavirus IgA antibody concentrations (refer Appendix F). The assay cut-off is 20 U/ml.

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

Table 3 presents the laboratory assays with their cut-off.

Table 3 Laboratory Assays

Antibody	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Core Laboratory
Rotavirus IgA	ELISA	In-house	U/ml	20	GSK Biologicals, Rixensart*

ELISA: Enzyme-linked immunosorbent assay
U/ml: units/millilitre
* GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals

5.6.3. Immunological read-outs

Table 4 presents the immunological read-outs for the study.

Table 4 Immunological read-outs

Sampling time point			Marker	Number of subjects
Timing	Month	Visit number		
Serology (in a subset of subjects [N = 60])				
Pre	Day 0	1	HRV IgA	60
Post-vacc 2	Month 2	3	HRV IgA	60
GE stool analysis				
From Visit 1 to Visit 5			RV antigen	All

Additional analysis (Amended, 07 May 2007)

If deemed necessary by the investigator, additional analysis on other tissues/fluids (e.g. cerebrospinal fluid in case of meningitis) may be performed by GSK Biologicals' designated laboratory.

Samples will not be labelled with information that directly identifies the subjects but will be coded with the identification number for the subject.

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests.

It may be that any findings in the present study necessitates further investigation by GSK Biologicals into the efficacy or immunogenicity of the HRV vaccine and its constituents under study.

Refer also to protocol Appendix B, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

6. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

The lyophilised formulations of HRV vaccine/Placebo to be used has been developed and manufactured by GSK Biologicals. The Quality Control Standards and Requirements for the candidate vaccine are described in separate release protocols and the required approvals have been obtained.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

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Table 5 gives the detailed formulation of the HRV vaccine/Placebo.

Table 5 Composition of the GSK Biologicals' HRV lyophilised vaccine and Placebo

Vaccine	Formulation	Presentation	Volume
LYOPHILISED FORMULATION			
GSK Biologicals' HRV lyophilised vaccine	RIX4414 HRV strain at least $10^{6.0}$ $CCID_{50}$ Dulbecco's Modified Eagle Medium (DMEM) 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised vaccine in a monodose glass vial Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' Placebo for HRV lyophilised vaccine	DMEM 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised Placebo in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals. calcium carbonate buffer	Calcium carbonate 60 mg/ml Xanthane 0.25% in 1.0 ml water for injection	Liquid buffer in prefilled syringe	at least 1.1 ml

Refer Appendix G for details of vaccine supplies.

6.1. Dosage and administration

6.1.1. Lyophilised formulation of HRV vaccine/Placebo

To prepare GSK Biologicals' HRV lyophilised vaccine/Placebo for administration, the entire content of the supplied diluents (calcium carbonate buffer) should be transferred from the oral applicator into the vial of the lyophilised product (HRV vaccine/Placebo) via the intermediate device. The vial should be shaken well to resuspend the vaccine. The entire volume of the resuspended product (approximately 1 ml) should be withdrawn into the same oral applicator and the resuspended product should then be administered promptly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration should occur in a quiet environment. Sufficient time should be allowed for the baby to swallow the vaccine/Placebo, to avoid regurgitation or vomiting. Should however 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 in the study.

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.

The vaccination regimen is summarised in Table 6.

Table 6 Dosage and Administration

Visit	Vaccination	Dose	Vaccine	Route
1, 2	Rotavirus/Placebo	1	Lyophilised HRV vaccine/ Placebo	Oral

All vaccines administered should be documented in the eCRF.

6.2. Storage

All investigational products to be administered to subjects must be stored in a safe and locked place with no access by unauthorised personnel.

Vaccines will be stored at the defined temperature range (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 monitoring device will be used as a back up device and it will be opened in case of any 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 monitoring device), 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 after the alarm is activated.

It is also required to place a validated freezing point indicator 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.

6.3. Vaccine accountability

The head of the medical institution is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the head of the medical institution or the storage manager must maintain investigational product accountability records throughout the course of the study. The storage manager will document the amount of investigational product received from and returned to GSK, the amount supplied and/or administered to and returned by subjects, if applicable. For more details see Appendix G.

6.4. Treatment allocation and randomisation

Target enrolment will be 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the Placebo Group) to obtain 612 evaluable subjects (408 subjects in the HRV lyophilised vaccine group and 204 subjects in the Placebo Group) for the evaluation of the primary objective.

The actual treatment number used for first vaccination of the subject must be recorded by the investigator in the eCRF (Randomisation/Treatment Allocation Section).

6.4.1. Randomisation of supplies

A randomisation 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 randomisation 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, 5% over-randomisation of supplies will be prepared.

The vaccine doses will be distributed to each study centre, respecting the randomisation block size.

6.4.2. Randomisation of subjects

The treatment allocation at the investigator site will be performed using a central randomisation system on Internet (SBIR). The randomisation algorithm will use a minimisation procedure accounting for centre.

After having checked that a subject is eligible, the person in charge of the vaccination will access the randomisation system on Internet. Upon providing a subject number for

the subject, the randomisation system will use the minimisation algorithm to determine the treatment number to be used for the subject.

Would internet be unavailable the subjects would be administered the vaccine number with the highest number still available at the vaccination site.

6.4.3. Subset for immunogenicity

A subset of 60 subjects will be part of the immunogenicity subset. Due to foreseeable difficulty in obtaining consent for withdrawal of blood from subjects, only those subjects whose parents/guardians consented will be enrolled in this immunogenicity subset. This subset will be centre specific and not all the centres will enrol subjects in to this subset. All subjects in this subset will provide blood samples to explore immunogenicity of the HRV vaccine/Placebo.

6.5. Method of blinding and breaking the study blind

The study will be conducted in a double-blind manner with respect to HRV vaccine and placebo. The parents/guardians of the subjects, the study personnel and the investigator will be unaware of the study vaccine administered (HRV vaccine or placebo). Blinding will be maintained for the whole study period. If the final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period, access to the individual treatment decode during the final analysis will be limited to the statistician and the database administrator to maintain double blinding until study end. This will allow unbiased evaluation of the study vaccine.

The investigator, or person designated by the investigator, should contact GSK Biologicals' Central Safety physician directly or via the local safety contact (see below and Study Contact for Emergency Code Break in Sponsor Information page) to discuss the need for emergency unblinding. The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) 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.

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any serious adverse event (SAE) report associated with the use of the investigational product, which is unexpected and attributable/suspected, prior to regulatory reporting. The Clinical Safety physician is responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (Refer to Section 8.9).

GSK Biologicals Clinical Safety Physician (Study Contact for Emergency Code Break)
Tel: [redacted] Fax: [redacted] or [redacted] Mobile phones for 7/7 day availability: [redacted] (Head Safety Evaluation and Risk Management Paediatric) Back-up mobile phone contact: [redacted]

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-randomisation 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 randomisation 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 randomised 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 31 days after each dose of study vaccine 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 or at any time during the study period up to Visit 3 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.

Any vaccine not foreseen in the study protocol administered since birth up to Visit 3 is 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 [Axillary temperature <37.5°C (99.5°F)] 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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form. Refer to Section 8.2 for definition of SAE.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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.

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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.

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 vaccination) should be recorded in the medical history section of the subject's eCRF.

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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 hospitalisation or prolongation of existing hospitalisation,

NOTE: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation 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 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 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 hospitalisation.

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. vital signs) 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. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not 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 HRV vaccine/Placebo must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity 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 intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at randomisation or the first receipt of the HRV vaccine/Placebo and will end at the last study visit (i.e. Visit 5) following administration of the last dose of the HRV vaccine/Placebo for each subject. See Section 8.8 for instructions for reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

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The investigator will inquire about the occurrence of AEs/SAEs at every visit/contact during the study and throughout the follow-up phase as appropriate.

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.

When an AE/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/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/SAE screens in the eCRF. 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.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.8.2 for details of the back-up reporting system.

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8.5.1. Solicited adverse events

Solicited general AEs

Solicited adverse events will be evaluated during an 8-day follow-up period (Day 0 to Day 7) after each HRV vaccine/Placebo dose. Diary cards will be provided to the parents/guardian's of the subject to record the symptoms observed.

The general adverse events solicited in this study is listed below

Fever (axillary)
Irritability/Fussiness
Diarrhoea
Vomiting
Loss of appetite
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 7:

Table 7 Intensity scales to be used by the parents/guardians for solicited symptoms

Adverse Event	Intensity grade	Parameter
Fever*		Record temperature in °C using an 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
Diarrhoea¶		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 ≥ 37.5°C as measured by an axillary thermometer.
¶Diarrhoea 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 diarrhoea, fever and vomiting occurring during the solicited 8-day follow-up period will be scored at GSK Biologicals as described in Table 8.

Table 8 Intensity scales used at GSK Biologicals' for diarrhoea, vomiting and fever reported during the solicited follow-up period

Adverse Experience	Intensity grade	Parameter
Diarrhoea	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	Temperature axillary < 37.5°C
	1	Temperature axillary ≥ 37.5 – ≤ 38.0°C
	2	Temperature axillary > 38.0 – ≤ 39.0°C
	3	Temperature axillary > 39.0°C

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

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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 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 utilised 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 submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information 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.

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Causality of all other AEs should be assessed by the investigator using the following question:

"Is there a reasonable possibility that the AE (or SAE) may have been caused by the investigational product?"

NO	:	The AE 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.
YES	:	There is a reasonable possibility that the vaccine contributed to the AE.

When new information is received, the causality will be reviewed and updated, if necessary.

A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. 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 (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.

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, if applicable
- Erroneous administration
- Other cause (specify).

8.6.3. Medically attended visits

For each solicited and unsolicited symptom the subject experiences (including gastroenteritis), the subject's parents/guardians will be asked if the subject 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 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 AEs 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, stabilised, 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 recognised 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 screens in the eCRF. The updated screens in the eCRF should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.8.1.

For cases of IS, the investigator will document all available information on the Serious Adverse Event pages contained in the individual eCRF, as well as on the IS form.

The Standard Verbal Autopsy Questionnaire (see Appendix H) [World Health Organization] should be completed whenever possible 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 an autopsy is performed or not. The Standard Verbal Autopsy Questionnaire does not replace the written autopsy report.

In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.8.2. for details of the back-up reporting system.

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Outcome of any non-serious AE 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

The SAE screens in the eCRF will be the primary method for reporting SAEs to GSK Biologicals during the study period. In case the electronic SAE reporting system does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs.

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 will complete and submit relevant information on the SAEs in the SAE screens in eCRF **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 completed and submitted in the SAE screens in eCRF within 24 hours of receipt of such information

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will fax the SAE reports to GSK Biologicals' Central Safety for Serious Adverse Event Reporting via a GSK local operating company. During the study, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours) and before using it to report additional 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, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours as outlined in Section 8.8.1. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. 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 SAE screens in eCRF. The SAE screens in eCRF should be updated when additional information is received 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.

When paper SAE Report Form is used as back-up system (if electronic SAE reporting system does not work or after freezing of the subject's eCRF), the investigator will report relevant information on SAEs to GSK within the 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, 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. When occurring during the study period, the investigator should update the SAE screens in eCRF once the electronic system is working again (and not later than 24 hours). When additional information is received on a SAE reported to GSK using the back-up paper SAE Report Form during the study period, the electronic system should be used to report the additional information WITHIN 24 HOURS if the electronic system is working again and only after updating the SAE screens in eCRF once the electronic system was working again.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper 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.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used) as outlined in Section 8.8.1.

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF/sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

Study Contact for Reporting SAEs
GlaxoSmithKline K.K Development & Medical Affairs Division, Sec. 2, Clinical Monitoring Dept. 2 [redacted] 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo 151-8566 Tel: [redacted] Fax: [redacted] Mobile phone for 7/7 day availability: [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] (Head Safety Evaluation and Risk Management Paediatric) 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 fulfil specific regulatory and 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 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.

After freezing of the subject's eCRF, if SAE follow-ups or new SAEs have to be reported, the investigators or designate should use paper SAE Report Forms and the facsimile (Fax) system.

8.11. 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.

8.12. Assessment of GE episodes leading to a medical intervention

Any GE episode (defined as diarrhoea with or without vomiting) leading to a medical intervention 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 temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given. 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 doctor visit, emergency room visit or hospitalisation) will also be recorded for each GE episode.

In the 20-point scoring system, points will be 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 will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 9.

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Table 9 The 20-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	2
≥ 6	3
Maximum number of looser than normal stools /24 hours	
1-3	1
4-5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2-4	2
≥ 5	3
Fever*	
Axillary	
36.6 – 37.9°C	1
38.0 – 38.4°C	2
≥ 38.5°C	3
Dehydration	
1-5%	2
≥ 6%	3
Treatment	
Rehydration	1
Hospitalisation	2

* 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.

Periodic contact will be made with the subjects' family to enquire about the occurrence of GE leading to a medical intervention. Collection of a stool sample will be requested if not yet provided and if GE occurred since last contact. For an GE considered to be an SAE, the SAE screen/form in the eCRF is completed.

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.

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9.2. Subject withdrawal

Subjects who are withdrawn because of 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 8.7).

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/was not available for 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 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

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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 leading to medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

10.2. Secondary endpoints

Efficacy

- Occurrence of severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.
- Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- Occurrence of any RV GE and severe RV GE leading to medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

- 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/Placebo.
- Occurrence of unsolicited adverse events within 31 days (Day 0 to Day 30) after any dose of HRV vaccine/Placebo according to Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of serious adverse events throughout the study period.

Immunogenicity (in the immunogenicity subset N = 60)

- Serum anti-rotavirus IgA antibody concentration at Visit 3.
- Seroconversion in terms of anti-rotavirus IgA antibody at Visit 3.

10.3. Estimated sample size

The primary objective is to determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Target enrolment will be 765 subjects (510 subjects in the HRV lyophilised vaccine group and 255 subjects in the Placebo Group) to obtain 612 evaluable subjects (408 subjects in the HRV lyophilised vaccine group and 204 subjects in the Placebo Group) with an attrition rate of 20% of non-evaluable subjects for the evaluation of the primary objective.

Considering a 2:1 randomisation ratio and various incidence rates, Table 10 provides the power that the 95% CI for vaccine efficacy (VE) will be above 0% and 10%.

Therefore, for an 8% attack rate (AR) of RV GE leading to a medical intervention in the Placebo Group from 2 weeks after Dose 2 up to 2 years of age, and if the VE is truly 80%, the study has 92% power to observe a 95% CI for the VE that will be above 10%. It is expected to observe a total of 28 RV GE leading to a medical intervention during the efficacy follow-up period in the Total Vaccinated Cohort.

In Japan, medical intervention risk due to RV GE is reported in 50% of children until 6 years of age which is not the school age. Supposing that the 50% risk is observed every year, it can be calculated that AR of the annual RV GE is 8.3% (50/6). The RV GE cases reported in 2005/2006 season seems to be low compared with those in past years. We have estimated that AR of RV GE during the 2 years is 8% considering yearly fluctuation of AR.

Table 10 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 612 evaluable subjects - 408 subjects in HRV group and 204 subject in the Placebo Group, power based on 1.000 simulations using Proc StatXact)

Incidence rate in the Placebo for any RV GE leading to a medical intervention	VE (%)	Power to have a lower limit of the 95%CI on VE ≥ 0%	Power to have a lower limit of the 95%CI on VE ≥ 10%
10%	80%	97%	96%
	70%	90%	83%
8%*	80%**	94%	92%
	70%	82%	74%
7%	80%	90%	86%
	70%	75%	67%
5%	80%	76%	69%
	70%	59%	50%

* anticipated rate in the Placebo for any RV GE leading to a medical intervention
**anticipated vaccine efficacy

10.4. Study cohorts to be evaluated

10.4.1. 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 from the immunogenicity subset for whom immunogenicity data are available.
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects.

10.4.2. ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects:

- who received two 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,
- who had no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks after Dose 2 of HRV vaccine or placebo,
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

10.4.3. 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,
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol.

10.4.4. 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 time point.
- 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 10.5 for definition of seronegative subjects.

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 vaccinated 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 vaccinated subjects are excluded from the ATP immunogenicity cohort. In such a case, the total vaccinated cohort analyses will evaluate whether exclusion from the ATP cohort could have biased the results.

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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.

Safety

Subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be re-assessed to ensure more accurate reporting of study data by further analysis.

Immunogenicity

The cut-off value of anti-rotavirus IgA antibody is defined by the laboratory before the analysis and is described in Section 5.6.2.

- A seronegative subject is a subject whose titre is below the cut-off value.
- A seropositive subject is a subject whose titre is greater than or equal to the cut-off value.
- Seroconversion is defined as the appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/millilitre (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine) seronegative.

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.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced.

10.6. Final analyses

Final analysis will be done when 28 RV GE episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV GE leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

10.6.1. Analysis of demographics

The mean, range and standard deviation of height in centimetre (cm), weight in kilogram (kg) and of age in weeks will be calculated per group. The racial and gender composition per group will also be presented.

The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group.

Summary of feeding practice 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 against:

- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to G1 serotype caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and due to non-G1 serotypes during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE of any aetiology leading to a medical intervention, efficacy against hospitalisation due to GE of any aetiology, efficacy during the period starting from two weeks after Dose 2 until Visit 4).

10.6.3. Analysis of safety

The overall incidence, with exact 95% CI, of any adverse events (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each 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.

The verbatim reports of unsolicited adverse events will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will

be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited adverse events occurring within 31-day follow-up period after any doses with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited adverse events rated as grade 3 and for unsolicited adverse events with causal relationship to vaccination.

Serious adverse events reported during the study period will be described in detail.

10.6.4. Analysis of immunogenicity

In a subset of subjects (N = 60)

For each treatment group, at each time point that anti-rotavirus IgA is measured,

- Seroconversion/seropositivity and their exact 95% CI will be calculated.
- GMCs 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 (RCCs).

The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between HRV vaccine and Placebo groups will be computed.

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. STUDY PERIOD

May 2007 –December 2009.

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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 aetiology 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 recognised 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.

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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 minimise 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 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 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

A Deviations from Protocol

The investigator/sub-investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without agreement by the sponsor or prior IRB approval. As soon as possible, the implemented deviation or change and the reasons for it should be submitted to the head of the medical institution and the IRB for approval, and via the head of the medical institution to the sponsor for agreement.

The investigator/sub-investigator should document and explain any deviation from the approved protocol, submit the document and retain its copy.

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B Changes of Protocol

1. If it becomes necessary to make any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects, the sponsor should promptly document the changes and reasons for them and amend the protocol after discussion with the coordinating investigator and the medical expert, and notify the heads of the medical institutions and investigators of the changes of the protocol (sample informed consent form and other written information, if necessary). The investigator should not implement any significant changes without approval from the IRB.
2. For changes other than the above 1), the sponsor should document the changes and reasons for them and inform the heads of the medical institutions and investigators of the changes of the protocol. Such changes require prior approval from the IRB, except where necessary to eliminate an immediate hazard(s), or when the change(s) involves only logistical or administrative aspects of the study. The investigator should promptly report the changes implemented without prior approval to the IRB for approval.
3. 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.
4. Submission of 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 amendment before it can be implemented will depend on local regulatory requirements.

III. Sponsor's Termination of Study

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator and site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicentre studies, this can occur at one or more or at all sites. If GSK determines such action is needed, GSK will discuss this with the investigator and the head of the medical institution, including the reasons for taking such action, at that time. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

GSK will promptly inform all other investigators and the head of the medical institution, and/or institutions conducting the study if the study is suspended or terminated for safety reasons. GSK will also promptly 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 and the head of the medical institution must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

Reasons for suspension or early termination will be documented in the study file at GSK Biologicals. 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

By monitoring the parties involved in the study including medical institutions, investigators, sub-investigators, study collaborators, and storage managers, monitors:

1. Oversee the process of obtaining written informed consent, the control of investigational products and the progress of the study (including withdrawals and adverse events, and ensure that the conduct of the study is in compliance with the "Good Clinical Practices" (GCP) (MHW Ordinance No.28 dated 27 March 1997), this protocol, and any other written agreement between the sponsor and the investigator/institution.
2. Collect and provide information that is necessary to conduct the study properly (information on investigational products' safety, efficacy and quality).
3. Verify that the investigator has adequate qualifications and resources and remain adequate throughout the study period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the study and remain adequate throughout the study period.
4. Verify that source documents and other study records are accurate, complete, kept up-to-date and maintained.
5. Determine whether the person responsible for retaining records is maintaining the essential documents at each medical institution.
6. Check the accuracy and completeness of the eCRF entries, source documents and other study-related records against each other.

7. The monitor will perform an eCRF review and a Source Document verification (verify eCRF/RDE entries 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).
8. 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.
9. Make clarifications to eCRFs in accordance with the standard clarification agreement (SCA).

The investigator and institution should agree to allow the monitor direct access to essential documents and other relevant documents. Direct access to essential documents by monitors and the scope of those documents will be specified separately in the written procedures for monitoring prepared for this study. Details of the standard clarification agreement (SCA) will be specified separately in the written procedures for SCA discussed and approved by the monitor and the investigator.

VI. Archiving of Data

A Records Retention

Following closure of the study, the investigator or the head of the medical institution (if applicable) 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).

The persons responsible for retaining records designated by the medical institution should maintain essential documents, including subject's medical records, laboratory data, records of IRB review, contract, records of informed consent, and records of investigational products control at the medical institution as required by the GCP for one of the following periods 1) or 2), whichever is longer. However, if the sponsor needs to retain these documents for a longer period, the period and methods of retention should be discussed with the sponsor. The person responsible for retaining records will be designated for each type of records. The sponsor will inform the head of the medical institution in writing as to when these documents no longer need to be retained.

1. until manufacturing (import) approval is granted on the investigational product (or for 3 years after the formal discontinuation of clinical development of the investigational product)
2. for 3 years after discontinuation or completion of the study

B Provision of Study results and Information to Investigators

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, GSK will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the subjects, as

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appropriate. In addition, the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at a GSK site or other mutually agreeable location.

GSK will provide the investigator with the randomization codes for their site after the statistical analysis for the entire study has been completed.

VII. Data Management

Subject data are collected by the investigator or designee using the eCRF defined by GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Any change or correction to eCRF entries will be made through the Data Clarification Request (DCR) if such action is needed after the eCRF is retrieved by GSK. Database freeze will occur when data management quality control procedures are completed. Original eCRFs and DCRs will be retained by GSK, while the investigator will retain a copy.

Data management staff may make clarifications to eCRFs as defined in the SCA. Details of the SCA will be specified separately in the written procedures for SCA discussed and approved by the monitor and the investigator.

VIII. Quality Control, Quality Assurance and Audits

A Quality Control

The sponsor's sections involved in the study, including monitoring, archiving, investigational product control, data management, and statistical analysis will perform quality control in compliance with their respective standard operating procedures prepared by the sponsor, and maintain records of quality control.

B Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

C 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's 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.

IX. 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.

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Appendix C Overview of the Recruitment Plan

- The study will be conducted in multiple centres in Japan.
- Target enrolment will be 765 eligible subjects.
- Recruitment will be terminated when 765 eligible subjects have been enrolled.
- The intended duration of the study, per subject, will be till the time that the subject is two years of age.
- 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 (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. 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**

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 minimise the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. **Serum separation**

These guidelines aim to ensure high quality serum by minimising 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. 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).

3. **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.

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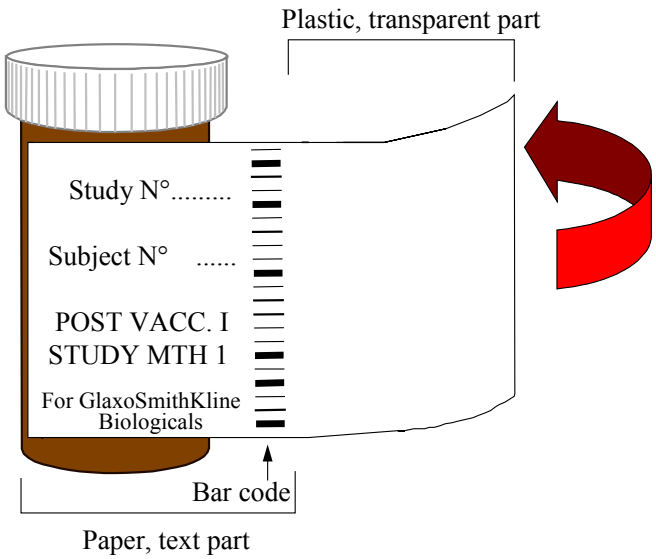
- The label should be attached to the tube as follows (see diagram):
  - first attach the paper part of the label to the tube
  - then wrap the label around the tube so that the transparent, plastic part of the label overlaps with the label text and bar code and shields them.

This will ensure optimal label attachment.



- Labels should not be attached to caps.

4. **Sorting and storage**

- Tubes should be placed in the 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 Biological 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 serum samples.
- Once shipment 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 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.

1. Collection

Containers/8 ml tubes/ziplock bags and fridge envelopes will be provided to parents/guardians for collection of stool samples for planned stools subset and during any GE episodes. Parents/guardians will be asked to preferably use the containers to collect

[1] The Biological Specimen 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.

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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/8 ml tubes/ziplock bag label with a black ink or ballpoint pen and return the collected stool samples to the study personnel. Subject number will be used for stool sample identification.
- If necessary, any hand-written additions to the labels by the study personnel should be made using indelible ink.

3. Preparation of aliquots

- Stool samples collected during gastroenteritis episode leading to medical attention will be processed at study site/local laboratory to prepare aliquots in 8ml tubes. Please note, if sufficient stool sample is available a back-up sample should be retained at the study site.

4. Sorting and storage

- The stool 8 ml tubes 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 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.
- 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.

GLAXOSMITHKLINE BIOLOGICALS

Biospecimen reception
Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart – Belgium

Telephone: [redacted]

Fax: [redacted]

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Appendix E Shipment of Biological Samples

Instructions for Shipment of Serum/Stool Samples

Biospecimen 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.

Biospecimen samples must be placed with dry ice (maximum -20°C) in a container complying with International Air Transport Association (IATA) requirements if shipment by air or complying with ADR or local regulations if transport by road. The completed standard Biological Specimen 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).

The airway bill should contain the instruction for storage of samples at maximum -20°C.

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.

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]

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Appendix F Laboratory Assays

Serum Analysis

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 H_2SO_4.

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 millilitre (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 et al. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet. 1999; 354:287-90.

GE stool analysis

1. Antigen Detection in GE stool samples

Rotavirus antigen in GE episodes will be detected by ELISA.

2. RV strain typing

Targeted RV gene will be amplified by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) to generate RV cDNA fragments. The genotype will be confirmed by reverse hybridization using serotype-specific DNA probes and/or by direct sequencing of the amplified RV cDNA product.

This genotyping analysis can be completed with the determination of the P-genotype 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 study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol.

- HRV vaccine in monodose vials.
- Placebo in monodose vials.
- Diluent (calcium carbonate buffer) in pre-filled syringes.

At least 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).

Additional doses will also be supplied for over-randomisation.

All monodoses vials/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 time point. Each label will contain the following information: study number, identification number for the subject , sampling time point , and timing .

Other supplies provided by GSK Biologicals:

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:

- tubes with screw caps for serum samples,
- racks and cardboard boxes for the tubes of serum.
- Supply for stool collection

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 from local country medical department to investigational site**

Upon reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

Attention of Clinical Trial Supplies Unit
GSK Biologicals Rixensart
Fax : [redacted]
E-mail: [redacted]

In case of any temperature deviation, the official written approval for the use of vaccine must be obtained from GSK.

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 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 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 GSK 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.

Appendix H Standard Questionnaire for Verbal Autopsy

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).

The document is supplied as a separate PDF file.

Appendix I Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007
Co-ordinating author:	[redacted]
Rationale/background for changes: The protocol has been amended as per the request from Pharmaceutical and Medical Devices Agency (PMDA), Japan.	
Text has been deleted in the following section: **Section 5.6.3: Immunological read-outs:** **Additional analysis:** This may include the management of the quality of these current tests, the maintenance or improvement of these current tests. ~~the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.~~ It may be that any findings in the present study ~~or in other studies~~ necessitates further investigation by GSK Biologicals into the efficacy or immunogenicity of the ~~vaccine.~~ HRV vaccine and its constituents under study. ~~or further research in the disease under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.~~ ~~A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.Any sample testing will be done in line with the consent of the individual subject's parents/guardians.Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.~~	

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GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007

Approved by:

Director,
Worldwide Clinical Development,
Rotavirus vaccine, [redacted] dd-mm-yyyy

Deputy Director,
Clinical Development,
GlaxoSmithKline K.K. [redacted] dd-mm-yyyy

For internal use only
----------Checksum----------!Ver.!Created On
20f83eacb735d614aa670c92c5638187 2.2 11/05/2007
b0372337c2c916c62a16bf4680dcb6c9 1.0 11/05/2007
20f83eacb735d614aa670c92c5638187 2.2 11/05/2007

Annex 2

Standard Verbal Autopsy Questionnaire

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

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Rota-056 (107625)

GlaxoSmithKline

Sponsor:
GSK Building
6-15, Sendagaya 4-chome
Shibuya-ku, Tokyo 151-8566
Japan

Study vaccine number	444563
Study vaccine	Lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	107625 (Rota-056)
Date of approval	Final: 30 March 2007
Title	Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Rotavirus Vaccine • [redacted] Central Study Co-ordinator • [redacted] Central Study Co-ordinator • [redacted] Statistician • [redacted] Manager, Clinical Development

Approval of Sponsor signatories

Sponsor signatory: [redacted]

Director,
Worldwide Clinical Development,
Rotavirus vaccine,
GSK Biologicals.

[redacted]

Deputy Director,
Clinical Development,
GlaxoSmithKline K.K.

Signature: [redacted]

Date: [redacted] 11 Apr 2007

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!f15f230730dc4fe3180b0437f1d72ae 1.2 10/04/2007

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Sponsor:
GSK Building
6-15, Sendagaya 4-chome
Shibuya-ku, Tokyo 151-8566
Japan

Study vaccine number	444563
Study vaccine	Lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number and abbreviated title	107625 (Rota-056)
Date of approval	Final: 30 March 2007
Title	Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants.
Detailed Title	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Co-ordinating author	[redacted] Scientific Writer
Contributing authors	• [redacted] Director, Rotavirus Vaccine • [redacted] Central Study Co-ordinator • [redacted] Central Study Co-ordinator • [redacted] Statistician • [redacted] Manager, Clinical Development

Approval of Sponsor signatories

Sponsor signatory:

[redacted]
Director,
Worldwide Clinical Development,
Rotavirus vaccine,
GSK Biologicals.

[redacted]
Deputy Director,
Clinical Development,
GlaxoSmithKline K.K.

Signature:

Date: [redacted] 12 April 2007

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1f15f230730de46e3180b0437f4d72ae 1.2 10/04/2007

GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
ROTA-056	107625

***Date:* 14 October 2009**

Concerns: Protocol Investigator Agreement

Details:

The original protocol was amended prior to submission to the investigators. Therefore Amendment #1 will be the only approval we have signed from investigators in our files.

Made by: [redacted] **Function: CTA**

(If required) Approved by: [redacted] **Approver's Signatu** [redacted]

Function *[Line Manager]*:_____ **Signature Date:** [redacted]2009

Appendix I Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number and abbreviated title	107625 (Rota-056)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.
Amendment number:	1
Amendment date:	07 May 2007
Co-ordinating author:	[redacted]
Rationale/background for changes: The protocol has been amended as per the request from Pharmaceutical and Medical Devices Agency (PMDA), Japan.	
Text has been deleted in the following section: **Section 5.6.3: Immunological read-outs:** **Additional analysis:** This may include the management of the quality of these current tests, the maintenance or improvement of these current tests. ~~the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.~~ It may be that any findings in the present study ~~or in other studies~~ necessitates further investigation by GSK Biologicals into the efficacy or immunogenicity of the ~~vaccine.~~ HRV vaccine and its constituents under study. ~~or further research in the disease under study. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.~~ ~~A GSK Biologicals Research & Development Position Paper is available which describes the rationale for and some examples of what these further investigations might include.Any sample testing will be done in line with the consent of the individual subject's parents/guardians.Any human pharmacogenetic testing will require additional separate consent from the individual subjects and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.~~	

CONFIDENTIAL

107625 (Rota-056)
Amendment 1

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**		
eTrack study number and abbreviated title	107625 (Rota-056)	
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.	
Amendment number:	1	
Amendment date:	07 May 2007	
Approved by: Director, Worldwide Clinical Development, Rotavirus vaccine,	[redacted]	14-05-2007 dd-mm-yyyy
Deputy Director, Clinical Development, GlaxoSmithKline K.K.	[redacted]	dd-mm-yyyy

For internal use only
----------Checksum----------!Ver.!Created On
20f83eacb735d614aa670c92c5638187 2.2 11/05/2007
b0372337c2c916c62a16bf4680dcb6c9 1.0 11/05/2007
20f83eacb735d614aa670c92c5638187 2.2 11/05/2007

CONFIDENTIAL

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

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Approved by:	
Director, Worldwide Clinical Development, Rotavirus vaccine,	[redacted] dd-mm-yyyy
Deputy Director, Clinical Development, GlaxoSmithKline K.K.	[redacted] 8 May 2007 dd-mm-yyyy

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20f83eacb735d614aa670c92c5638187 2.2 11/05/2007

GlaxoSmithKline

Note to File

Alias / Abbreviated Study Title	E-Track Study #
ROTA-056	107625

Date: ***14 October 2009***

Concerns: Protocol Investigator Agreement missing checksum

Details:

This File Note is to serve as documentation that the signed Japanese translated version of the Amendment 1 Protocol Investigator Agreement is missing the checksum.

Made by: [redacted] **Function:** CTA

(If required) Approved by: [redacted] **Approver's Sign** [redacted]

Function ***[Line Manager]:*** _____ **Signature Date:** 19 Oct 2009

GlaxoSmithKline

TRANSLATION COMPLIANCE FORM

--- Please fill in all sections of this form ----

Please insure that a written confidentiality agreement is available from the third party translators, when they undertake the translations.

Protocol N°: 107625 (Rota-056).....

Protocol Title: Efficacy, safety, reactogenicity and immunogenicity study of the lyophilised formulation of human rotavirus (HRV) vaccine 444563 in healthy Japanese infants

Translation(s) requested by: [redacted] .....**Date requested: 04-Feb-08**

Translation Reference N° (if applicable): .....

Document details:

Document details:	Unique document ID*	Date of original document	Language of original document	Translated language requested
Investigator Agreement(s) (Investigator signature page)				
[redacted]		18-May-07	Japanese	English
		29-May-07	Japanese	English
		29-May-07	Japanese	English
		15-Oct-07	Japanese	English
		21-May-07	Japanese	English
		14-May-07	Japanese	English
		05-Jul-07	Japanese	English
		07-May-07	Japanese	English
		21-Sep-07	Japanese	English

GlaxoSmithKline

[redacted]				
		16-Oct-07	Japanese	English
		28-May-07	Japanese	English
		07-May-07 08-May-07	Japanese	English
		07-May-07	Japanese	English
		23-May-07	Japanese	English
		14-May-07	Japanese	English
		11-May-07	Japanese	English
		30-Oct-07	Japanese	English
		10-May-07	Japanese	English
		15-May-07	Japanese	English
		09-May-07	Japanese	English
		10-May-07	Japanese	English

*Unique document identification: for exemple version N°, date, etc.

GlaxoSmithKline

Translation details:

- Name of translator: [redacted]
- Function of translator: Clinical Research Department 8
- Address of translator: 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo...
- Signature of translator: [redacted]
- Date of translation(s): 13 / Feb / 2008
  dd / mmm / yyyy

Review details:

This translation was/ these translations were reviewed for accuracy, consistency, and clarity with the original document(s) by:

- Name of reviewer: [redacted]
- Function of reviewer: Clinical Research Department 8
- Address of reviewer: 6-15, Sendagaya 4-chome, Shibuya-ku, Tokyo...
- Comments on translation(s):

(please document below any comments you may have on the translation(s) or if you feel further work on or re-work of the document(s) is necessary)

- Signature of reviewer: [redacted]
- Date of review: 14 / Feb / 2008
  dd / mmm / yyyy

Medical review and approval (if applicable according to local regulations):

- Name and function: .....
- Signature: .....
- Date: __ / ___ / ____
  dd / mmm / yyyy

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

eTrack study number and abbreviated title: 107625 (Rota-056)

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I agree to conduct properly the study in compliance with this protocol.

I agree ;

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Investigator

Date	2007/05/23
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/23
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/5/7
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/7
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/05/09
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/09
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/10
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/10
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/5/8
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/7
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

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Investigator

Date	2007/05/15
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/15
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/5/21
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/21
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

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Investigator

Date	2007/05/10
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/10
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

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Investigator

Date	2007/05/14
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/14
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/05/07
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/07
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/18
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/18
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/5/11
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/11
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/14
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/14
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

Title: A phase III, double-blind, randomized, placebo-controlled, multicentre study to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilized formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV, in Japan.

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Investigator

Date	2007/05/29
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/29
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/05/29
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/05/29
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

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Investigator

Date	2007/5/28
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/5/28
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/07/05
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/07/05
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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Investigator

Date	2007/10/15
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/10/15
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

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Investigator

Date	2007/10/16
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/10/16
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Investigator Agreement

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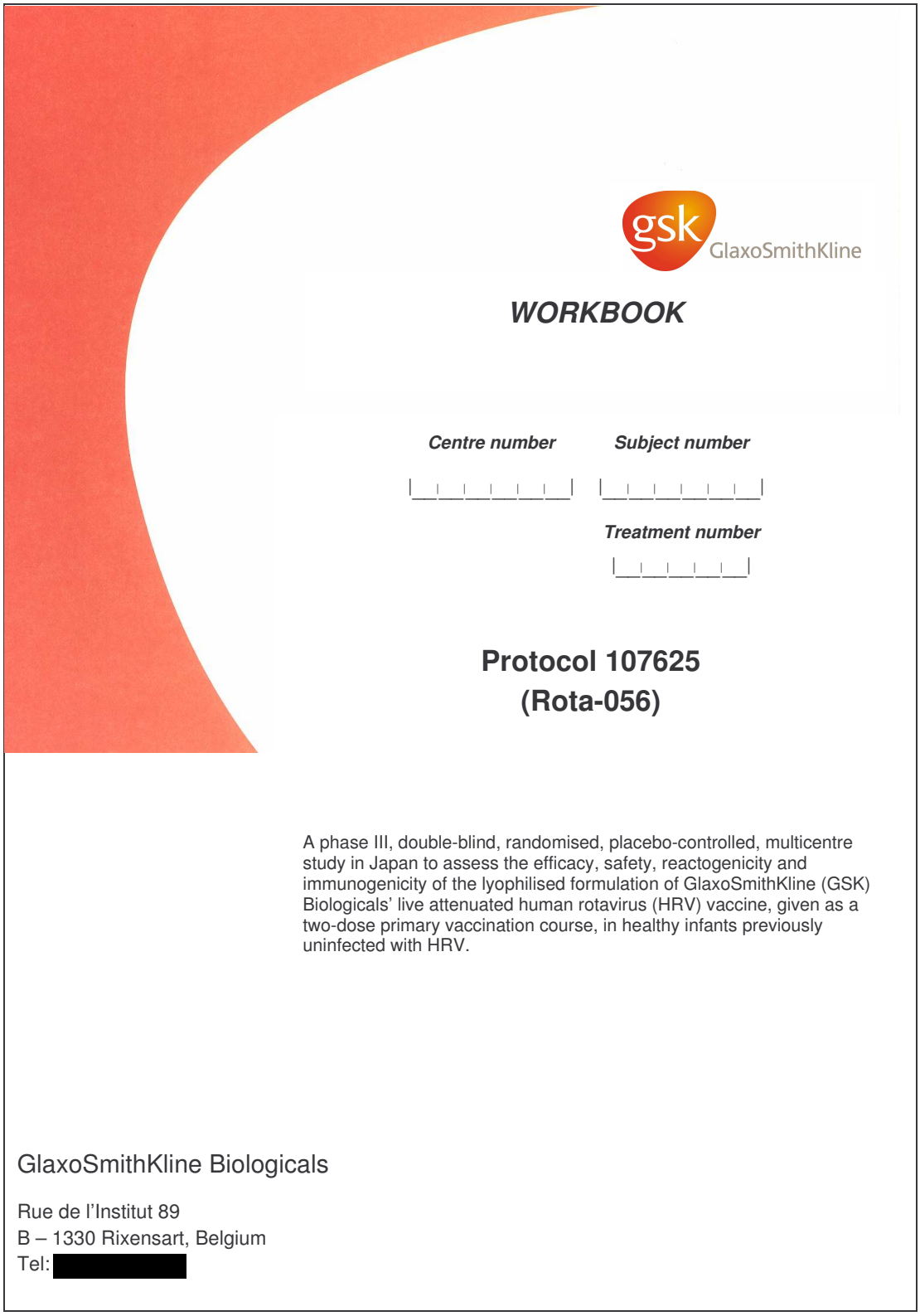
Investigator

Date	2007/10/30
Site Name	[redacted]
Department	[redacted]
Investigator Name	**(signature)** [redacted]

Sponsor: GlaxoSmithKline (Japan)

Date	2007/10/30
Department	Clinical Monitoring Department 2
Title	Department Manager
Name	**(signature)** [redacted]

Sample Case Report Form



GlaxoSmithKline

WORKBOOK

Centre number ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

Treatment number

|__|__|__|__|__|

Protocol 107625 (Rota-056)

A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

GlaxoSmithKline Biologicals

Rue de l'Institut 89
B – 1330 Rixensart, Belgium
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 | (day) | J A N | (month) | 2 0 0 6 | (year) = 1st January 2006

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** section(s) 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

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

Vomiting

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

Diarrhea:
Three or more looser than normal stools within a day.

Gastroenteritis [GE] episode is defined as diarrhea with or without vomiting.

ADVERSE EVENT DEFINITIONS

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: 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.
5: Fatal: AE is the cause of death (only applicable for SAE sections).

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 the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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107625 (Rota-056)

FLOW SHEET

Age	6-14 weeks			One year	Two years
Visits Timing Sampling time point	VISIT 1 Day 0 Pre-vacc	VISIT 2 Month 1	VISIT 3 Month 2 Post-vacc 2	VISIT 4	VISIT 5
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	●	●	-	-	-
Randomisation	●	-	-	-	-
Blood sampling (1 ml) for antibody determination in an immunogenicity subset *	●	-	●	-	-
Study vaccination (HRV vaccine/ Placebo)	●	●	-	-	-
Daily post-vaccination recording of solicited symptoms (Days 0–7) by parents/guardians	●	●	-	-	-
Return of reactogenicity diary card	-	○	○	-	-
Transcription of the reactogenicity diary card		●	●	-	-
Recording of unsolicited adverse events within 31 days (Day 0-Day 30) post-vaccination in all subjects, by investigator		●	●	-	-
Record any concomitant medication/vaccination, by investigator	●	●	●	●#	●#
Recording of Gastroenteritis [GE] leading to medical intervention occurring throughout the study period	●	●	●	●	●
Contact the subject's parent/gardian to check gastroenteritis [GE] occurrence at least every two weeks	○	○	○	○	○
Collection of stool samples if subject has Gastroenteritis [GE] leading to medical intervention	●	●	●	●	●
Return of gastroenteritis [GE] diary card	-	○	○	○	○
gastroenteritis [GE] diary card transcription	-	●	●	●	●
Recording of SAEs	●	●	●	●	●
Reporting AEs leading to drop-out	●	●	●	●	●
Conclusion at Visit 4				●	
Study conclusion	-	-	-	-	●

Note: Final analysis will be done when 28 RV gastroenteritis [GE] episodes leading to medical intervention and caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or when all subjects have reached two years of age, whichever is the earliest. If the number of cases of required RV gastroenteritis [GE] leading to medical intervention and caused by the circulating wild-type RV strains is reached before all subjects reach two years of age, an annex report will present the efficacy/safety data up to two years of age.

● is used to indicate a study procedure that requires documentation in the individual eCRF.

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

* Blood sampling will be done only from subjects in the immunogenicity subset (N = 60).

\# for concomitant medication administered for the treatment of an AE leading to drop-out/SAE.

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GlaxoSmithKline Biologicals

107625 (Rota-056)

FLOW SHEET

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed.

Intervals between study visits

Interval /Visit	Range of interval /Visit
Visit 1→Visit 2	30 - 48 days
Visit 2→Visit 3	30 - 48 days
Visit 4	1 year of age ± 15 days
Visit 5	2 years of age ± 15 days

N.B: The reference date for intervals between study visits: the first vaccination date

VISIT 1
DAY 0
6-14 weeks of age
DOSE 1

Informed Consent has to be obtained prior to any study procedure

GlaxoSmithKline Biologicals

107625 (Rota-056)

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.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids are allowed).

[C] Administration of immunoglobulin and/or any blood products during the study period.

[D] Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

The following adverse events (AEs) constitute absolute contraindications to further administration of HRV vaccine/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.

[A] Known hypersensitivity after previous administration of HRV vaccine or to any component of the vaccine.

[B] Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following AEs constitute contraindications to administration of HRV vaccine/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.

[C] Acute severe febrile illness.

[D] Diarrhoea or vomiting.

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107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**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

Did the subject agree that her/his biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the vaccine(s) or the disease(s) under study? ☐ Yes ☐ No ☐ NA

DEMOGRAPHICS

Center number: |__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender:
[M] ☐ Male
[F] ☐ Female

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: _____

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

1.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**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) should be enrolled in the study.

[2] ☐ A male or female infant 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/guardian of the subject.

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ Born between a gestation period of 36 and 42 weeks inclusive.

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 within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ History of use of experimental rotavirus vaccine.

[8] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs prior to the first vaccine dose. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)

[9] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract or other serious medical condition determined by the investigator.

[10] ☐ History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.

[11] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

2.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1**		|__|__|__|__|__|__|

ELIGIBILITY CHECK (continued)

EXCLUSION CRITERIA

[12] ☐ A family history of congenital or hereditary immunodeficiency.

[13] ☐ Uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

[14] ☐ 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. Axillary temperature <37.5°C.) Temperature greater than or equal to these cut-offs warrants deferral of the vaccination pending recovery of the subject.

[15] ☐ Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).

[16] ☐ Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

[17] ☐ Previous confirmed occurrence of RV gastroenteritis [GE].

[18] ☐ Concurrently participating in another clinical study, at any time during the study period in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number: |__|__|__|__|__|

3.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		VISIT 1		|__|__|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions, signs or symptoms present prior to the start of the study?

☐ 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.

4.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1**		|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken for serology?

☐ Yes → Date if different from visit date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

☐ No

☐ NA

5.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1** **DOSE 1**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|.|__| °C → Route: [A] ☐ **Axillary (mandatory)**
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Route**	**Has the study vaccine been administered according to the Protocol?**
[S] ☐ **HRV vaccine or placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral	☐ Yes ☐ No → *Please comment:* Comment: _____

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event
→ Please complete and submit **SAE** section
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete **Non-serious Adverse Event** section
→ Please specify AE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made 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** or a **Serious Adverse Event** section.

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box.

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

6.

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107625 (Rota-056)

Protocol				Subject Number
107625		DOSE 1		_____

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following signs/symptoms during the solicited period?

[U] ☐ Information not available
[NA] ☐ No Vaccine administered
[N] ☐ No
[Y] ☐ 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?	Medically attended visit	HO/ER/MD
Fever [FE] ☐ No ☐ Yes → °C: [A] ☐ **Axillary (mandatory)** [O] ☐ Oral [R] ☐ Rectal	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Cough/runny nose [CO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Fussiness/ Irritability [IR] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Loss of appetite [LO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Vomiting [VO] ☐ No ☐ Yes → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Fever:

Axillary	**≥ 37.5 °C**
Oral	≥ 37.5 °C
Rectal	≥ 38.0 °C

Medically attended visit:
(see protocol for full definition)
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 1**		|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS (DIARRHEA) (continued)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?		Causality?	Medically attended visit	
Diarrhea [DA] (*) ☐ No													
☐ Yes (**) → Number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please complete **Gastroenteritis Episodes Leading to a Medical Intervention** section in case of diarrhea leading to medical intervention. →If not leading to medical intervention, please complete date of last symptom: |__|__|__|__|__|__|__|__|	☐ No ☐ Yes	☐ No ☐ Yes→	HO/ER/MD |__|__|

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Medically attended visit:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel
(see protocol for full definition)

(*) Stool sample should be collected in case of diarrhea leading to medical intervention.

Stool Collection:

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

(**) If diarrhea leading to medical intervention, please complete the following items:
Medication for diarrhea?

☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: _____

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

8.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 1**		|__|__|__|__|__|__|

FEEDING PRACTICE (*)

- ☐ only breast-fed
- ☐ only formula-fed
- ☐ only solid food
- ☐ breast-fed and formula-fed
- ☐ breast-fed and solid food
- ☐ formula fed and solid food
- ☐ breast fed, formula fed and solid food

(*) *Please tick only one box*

Time between last feeding and administration of Dose 1: |__|__| hour |__|__| min

9.

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107625 (Rota-056)

Protocol				Subject Number
107625		**DOSE 1**		_____

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination?

[U] ☐ Information not available

[NA] ☐ No vaccine administered

[N] ☐ No

[Y] ☐ Yes → Fill in the **Non-Serious Adverse Event** section or **Serious Adverse Event** section as necessary.

10.

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VISIT 2

MONTH 1

30-48 Days after Visit 1

DOSE 2

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

GASTROENTERITIS LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 2**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for 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:
→ Please complete and submit **SAE** section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete **Non-serious Adverse Event** section.
→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

11.

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107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 2**	__ __ day __ __ __ month __ __ __ __ year	__ __ __ __ __ __

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention from Day 8 after Dose 1 of HRV vaccine or Placebo until Visit 2?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

12.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 2 DOSE 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|.|__| °C → Route: [A] ☐ **Axillary (mandatory)**
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Route**	**Has the study vaccine been administered according to the Protocol?**
[S] ☐ **HRV vaccine or placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral	☐ Yes ☐ No → *Please comment:* Comment: _____

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event
→ Please complete and submit **SAE** section
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete **Non-serious Adverse Event** section
→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made 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** or a **Serious Adverse Event** section.

If any **prophylactic** medication has been administered in anticipation of study vaccine reaction, please complete the **Medication** section and tick prophylactic box.

Any other **vaccines** administered during the study period must be recorded in the **Concomitant Vaccination** section.

13.

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107625 (Rota-056)

Protocol				Subject Number
107625		DOSE 2		_____

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following signs/symptoms during the solicited period?

[U] ☐ Information not available
[NA] ☐ No Vaccine administered
[N] ☐ No
[Y] ☐ 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?	Medically attended visit	HO/ER/MD
Fever [FE] ☐ No ☐ Yes → °C: [A] ☐ **Axillary (mandatory)** [O] ☐ Oral [R] ☐ Rectal	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	_ . _ ☐ not taken	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Cough/runny nose [CO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Fussiness/ Irritability [IR] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Loss of appetite [LO] ☐ No ☐ Yes → intensity:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__
Vomiting [VO] ☐ No ☐ Yes → number:	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	__ ___ ____	☐ No ☐ Yes	☐ No ☐ Yes →	__

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Fever:

Axillary	**≥ 37.5 °C**
Oral	≥ 37.5 °C
Rectal	≥ 38.0 °C

Medically attended visit:
(see protocol for full definition)
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

14.

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107625 (Rota-056)

Protocol				Subject Number
107625		DOSE 2		|__|__|__|__|__|__|

SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS (DIARRHEA) (continued)

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after day 7?		Causality?	Medically attended visit	
Diarrhea [DA] (*) ☐ No													
☐ Yes (**) → Number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please complete **Gastroenteritis Episodes Leading to a Medical Intervention** section in case of diarrhea leading to medical intervention. →If not leading to medical intervention, please complete date of last symptom: |__|__| |__|__|__| |__|__|__|	☐ No ☐ Yes	☐ No ☐ Yes→	HO/ER/MD |__|__|

Intensity: 0 / 1 / 2 / 3
(see Adverse Events definitions)

Medically attended visit:
HO: Hospitalization
ER: Emergency Room
MD: Medical Personnel
(see protocol for full definition)

(*) Stool sample should be collected in case of diarrhea leading to medical intervention.

Stool Collection:

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

(**) If diarrhea leading to medical intervention, please complete the following items:
Medication for diarrhea?

☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: _____

If any of these **adverse events** meets the protocol definition of **serious**, please complete and submit **Serious Adverse Event** section to GSK Biologicals Study Contact for SAE reporting within 24 hours.

15.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 2**		|__|__|__|__|__|__|

FEEDING PRACTICE (*)

- ☐ only breast-fed
- ☐ only formula-fed
- ☐ only solid food
- ☐ breast-fed and formula-fed
- ☐ breast-fed and solid food
- ☐ formula fed and solid food
- ☐ breast fed, formula fed and solid food

(*) *Please tick only one box*

Time between last feeding and administration of Dose 2: |__|__| hour |__|__| min

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107625 (Rota-056)

Protocol				Subject Number
107625		DOSE 2		_____

UNSOLICITED ADVERSE EVENTS

Has the subject experienced any serious or non-serious unsolicited adverse events within one month (minimum 30 days) post-vaccination?

[U] ☐ Information not available

[NA] ☐ No vaccine administered

[N] ☐ No

[Y] ☐ Yes → Fill in the **Non-Serious Adverse Event** section or **Serious Adverse Event** section as necessary.

17.

VISIT 3
MONTH 2

30-48 Days after Visit 2

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT 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 LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 3**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 3?

☐ Yes → Please complete the next pages.

☐ No → Please complete below and skip the following pages of this visit.

☐ 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:
→ Please complete and submit **SAE** section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete **Non-serious Adverse Event** section.
→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

18.

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107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 3**	__|__| __|__|__| __|__|__|__| day month year	__|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken for serology?

☐ Yes → Date if different from visit date: __\|__\| __\|__\|__\| __\|__\|__\|__\| day month year

☐ No

☐ NA

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention from Day 8 after Dose 2 of HRV vaccine or Placebo until Visit 3?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

19.

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VISIT 4

1 year of age ± 15 Days

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT 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 LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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107625 (Rota-056)

Protocol		Visit		Subject Number
107625		**VISIT 4**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 4?

☐ Yes → Please complete the next pages.

☐ No → Please complete below and skip the following pages of this visit.

☐ 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:

→ Please complete and submit **SAE** section.

→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section.

→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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107625 (Rota-056)

Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention between Visit 3 and 4?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4

EPISODE N°: |__|__|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: __________________________

Medical intervention: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (°C) → route: ☐ Axillary (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4 (continued)

EPISODE N°: |__|__|

Treatment?
- ☐ No
- ☐ Yes → ☐ Oral rehydration
  - ☐ IV rehydration
  - ☐ Oral and IV rehydration
  - ☐ Other, please specify: ___________________________

Medical intervention:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day month year)	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** → route: ☐ **Axillary** (*) ☐ Oral ☐ Rectal	
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION UP TO VISIT 4 (continued)

EPISODE N°: |__|__|

Treatment?
- ☐ No
- ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify: ___________________________

Medical intervention:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day / month / year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (°C)	→ route: ☐ Axillary (*) ☐ Oral ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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CONCOMITANT VACCINATION UP TO VISIT 4

Any vaccine not foreseen in the study protocol administered since birth up to Visit 3 is to be recorded with trade name, route of administration and date(s) of administration.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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Protocol				Subject Number
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CONCOMITANT VACCINATION UP TO VISIT 4

Have any vaccines other than the study vaccine(s) been administered as specified in the protocol up to visit 4?

☐ 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		

Route:

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

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**MEDICATION
UP TO VISIT 4**

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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

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 31 days after each dose of study vaccine 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 or at any time during the study period up to Visit 3 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 [Axillary temperature <37.5°C (99.5°F)] 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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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MEDICATION UP TO VISIT 4

Have any medications/treatments been administered as specified in the protocol up to Visit 4?

☐ 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					

26.

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 4

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS UP TO VISIT 4

(Please report **serious adverse events** only on the **Serious Adverse Event (SAE)** sections).

Has any **non-serious adverse events** occurred within **one month (minimum 30 days)** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages?

☐ No

☐ Yes, please complete the following table.

AE No.	**1**	**2**
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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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Protocol				Subject Number
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NON-SERIOUS ADVERSE EVENTS UP TO VISIT 4 (continued)

AE No.	3	4
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period (30 minutes)
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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: |__|__|

28.

CONCLUSION AT VISIT 4

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

SUBJECT STATUS AT VISIT 4

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 1 and Visit 4?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 1 and Visit 4?

☐ 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 a **Serious Adverse Event** section as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 1 and Visit 4?

☐ No ☐ Yes → Specify: _____

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Protocol				Subject Number
107625				|__|__|__|__|__|__|

SUBJECT STATUS AT VISIT 4 (continued)

Is the subject withdrawn at Visit 4?

☐ No

☐ Yes → Major reason for withdrawal (tick **one** box only).

☐ [SAE] Serious adverse event:
→ Please complete and submit SAE section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete Non-serious Adverse Event section.
→ Please specify AE No. |__|__| *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: _____

→ 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: _____

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VISIT 5

2 years of age ± 15 Days

REMINDERS

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)** section, 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.

MEDICATION/CONCOMITANT 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 LEADING TO A MEDICAL INTERVENTION

Please report any gastroenteritis leading to a medical intervention and stool collection in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

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Protocol		Visit		Subject Number
107625		**VISIT 5**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 5?

☐ Yes → Please complete the next pages.

☐ No → Please complete below and skip the following pages of this visit.

☐ 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:
→ Please complete and submit **SAE** section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete **Non-serious Adverse Event** section.
→ Please specify AE No. |__|__| *or* solicited AE code |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

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Protocol		Visit	Date of visit	Subject Number
107625		**VISIT 5**	____ ____ ____ day month year	_____

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION

Did the subject present gastroenteritis leading to medical intervention between Visit 4 and 5?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes Leading to a Medical Intervention** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes Leading to a Medical Intervention** section.

32.

GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION VISIT 4 TO 5

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Protocol				Subject Number
107625				|_|_|_|_|_|_|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION BETWEEN VISIT 4 AND VISIT 5

EPISODE N°: |__|__|

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical intervention:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Date (day month year)	Number of looser than normal stools per day	Number of vomiting per day	Temperature (℃) → route: ☐ Axillary (*) ☐ Oral ☐ Rectal	
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken
|_|_| |_|_|_| |_|_|_|_|	|_|_|	|_|_|	|_|_|_|.|_|	☐ not taken

(*) **route: axillary is mandatory.**

33.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION BETWEEN VISIT 4 AND VISIT 5 (continued)

EPISODE N°: |__|__|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical intervention: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day / month / year)	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)**	**→ route:** ☐ **Axillary** (*) ☐ Oral ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

GASTROENTERITIS EPISODE LEADING TO A MEDICAL INTERVENTION BETWEEN VISIT 4 AND VISIT 5 (continued)

EPISODE N°: |__|__|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical intervention: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical intervention: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| (day, month, year) |__|__|:|__|__| (hours, min)

Date (day, month, year)	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)**	→ **route:** ☐ **Axillary** (*) ☐ Oral ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|__|.|__|	☐ not taken

(*) **route: axillary is mandatory.**

35.

CONCOMITANT VACCINATION

VISIT 4 TO 5

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Have any vaccines other than the study vaccine(s) been administered between Visit 4 and 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		

Route:

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
IN	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

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MEDICATION
VISIT 4 TO 5

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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

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. Similarly, concomitant medication administered for the treatment of an SAE, at any time, must be recorded on the SAE Report Form.

Any investigational medication or vaccine administered throughout the study must be recorded in the eCRF.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments been administered between Visit 4 and 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					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

37.

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NON-SERIOUS ADVERSE EVENTS VISIT 4 TO 5

All AEs leading to subject withdrawal or drop-out must be recorded on the Adverse Event form in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report **serious adverse events** only on the **Serious Adverse Event (SAE)** sections).

Has any **non-serious adverse events** occurred between Visit 4 and 5 leading to drop-out?

☐ No

☐ Yes, please complete the following table.

AE No.	**51**	**52**
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

AE No.	53	54
Description:	_____ _____ _____	_____ _____ _____
For GSK		
Date Started:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Date Stopped:	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Maximum 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: |__|__|

39.

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STUDY CONCLUSION

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event between Visit 4 and 5?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken between Visit 4 and 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 a **Serious Adverse Event** section as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable between Visit 4 and 5?

☐ No ☐ Yes → Specify: _____

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107625 (Rota-056)

Protocol				Subject Number
107625				|__|__|__|__|__|__|

STUDY CONCLUSION (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** section.
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event:
→ Please complete **Non-serious Adverse Event** section
→ Please specify AE No. |__|__| *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: _____

→ 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: _____

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GlaxoSmithKline

107625 (Rota-056)

Protocol	Centre	
107625	|__|__|__|__|__|__|	

USE OF HUMAN SAMPLES BY GSK

In addition to the use of samples for the tests described in the protocol, samples might be used for other resarch by GSK (see protocol). Please tick what is also covered by the subject Informed Consent form of your center.

[2] ☐ **Quality Assurance of tests described in the protocol**

This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in the protocol as well as making sure that new tests are comparable to previous methods and work reliably.

[3a] ☐ **Further investigation by GSK Biologicals into the ability of HRV vaccine to protect people if any findings from related studies require it and further research in Rotavirus. These investigations excludes genetics and HIV testing.**

[3b] ☐ **Further investigation by GSK Biologicals into the ability of HRV vaccine to protect people if any findings from related studies require it and further research in Rotavirus. These investigations excludes genetic and HIV testing. Investigator will always ask in advance the permission of the independent Ethics Committee/Institutional Review Board linked to the institution where this research is performed.**

[4] ☐ **Further research by GSK Biologicals that is NOT RELATED to HRV vaccine or the Rotavirus done on an anonymous basis (meaning that any identification linking the subject to the sample is destroyed). This research excludes genetic and HIV testing and does not affect subject participation in the study.**

Please tick below box if a 15 years GSK storage period is covered by the subject's Informed Consent form of your center.

☐ **At least 15 years storage period by GSK Biologicals**

☐ **Other, specify:**_____

ICF Effective date: |__|__| |__|__|__| |__|__|__|__|
day month year

! Complete and submit a new form for each change during the study.

INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

1.

Template CRF version 12.4 – April 11, 2007

Protocol	DIARY CARD	DOSE 1	Subject number
107625 (Rota-056)	SOLICITED SYMPTOMS		|__|__|__|__|__|__|__|

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting, Diarrhea

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 axillary temperature every day. Please take temperature in the evening. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose	**Irritability / fussiness:**	**Loss of appetite:**
0:Normal	**0**:Behavior as usual	**0**:Normal
1:Cough/runny nose which is easily tolerated	**1**:Crying more than usual / no effect on normal activity	**1**:Eating less than usual / no effect on normal activity
2:Cough/runny nose which interferes with daily activity	**2**:Crying more than usual / interferes with normal activity	**2**:Eating less than usual / interferes with normal activity
3:Cough/runny nose which prevents daily activity	**3**:Crying that cannot be comforted / prevents normal activity	**3**:Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents > 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

SOLICITED SYMPTOMS	Day0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms Year month day
Date□	__/__	__/__	__/__	__/__	__/__	__/__	__/__	__/__		
Axillary Temperature → °C:	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	200|__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Whimpering (or Irritability/ Fussiness) → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	if ongoing after day 7 please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET
Stools samples taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

Stool collection date: |__|__| |__|__|__| |__|__|__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__|__| |__|__|__|__|__|__| hour: |__|__| min: |__|__|

☐**MEDICATION FOR DIARRHEA**☐ ☐**MEDICAL ATTENTION**☐

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: _____
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200|__||__|__||__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

Diary Card Template CRF Version 12.4, May 14 2007

PLEASE INFORM: ……..……. ☎: ……..……

Protocol	DIARY CARD	DOSE 2	Subject number
107625 (Rota-056)	SOLICITED SYMPTOMS		|__|__|__|__|__|__|__|

SOLICITED GENERAL SYMPTOMS

I. Temperature, Cough/runny nose, Irritability/Fussiness, Loss of appetite, Vomiting, Diarrhea

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 axillary temperature every day. Please take temperature in the evening. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose	**Irritability / fussiness:**	**Loss of appetite:**
0:Normal	**0**:Behavior as usual	**0**:Normal
1:Cough/runny nose which is easily tolerated	**1**:Crying more than usual / no effect on normal activity	**1**:Eating less than usual / no effect on normal activity
2:Cough/runny nose which interferes with daily activity	**2**:Crying more than usual / interferes with normal activity	**2**:Eating less than usual / interferes with normal activity
3:Cough/runny nose which prevents daily activity	**3**:Crying that cannot be comforted / prevents normal activity	**3**:Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents > 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

SOLICITED SYMPTOMS	Day0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Ongoing after Day 7?	Date of last Day of Symptoms Year month day
Date□	__/__	__/__	__/__	__/__	__/__	__/__	__/__	__/__		
Axillary Temperature → °C:	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	200|__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Whimpering (or Irritability/ Fussiness) → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	200|__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	if ongoing after day 7 please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET
Stools samples taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

Stool collection date: |__|__| |__|__|__| |__|__|__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__|__| |__|__|__|__|__|__| hour: |__|__| min: |__|__|

☐MEDICATION FOR DIARRHEA☐ ☐MEDICAL ATTENTION☐

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: _____
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200|__||__|__||__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

Diary Card Template CRF Version 12.4, May 14 2007

PLEASE INFORM: ……..……. ☎: ……..……

Protocol	DIARY CARD	DOSE 1	Subject number
107625 (Rota-056)	FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 7		|__|__|__|__|__|__|

SOLICITED DIARRHEA SYMPTOM If the symptom continues After 7 days

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 axillary temperature every day. Please take temperature in the evening. 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 continue after 7 day, please continue to assess the following Symptoms until the end of the diarrhea.
(*) If not already collected during the period from D0-D7, please collect stools samples in case of diarrhea leading to medical intervention.

SOLICITED DIARRHEA SYMPTOMS	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__
Axillary Temperature → °C:	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _
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

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__|

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |200|__||__|__| |__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ..... ☎: .....

Diary Card Template CRF Version 12.4, May 14 2007

Protocol	DIARY CARD	DOSE 2	Subject number
107625 (Rota-056)	FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 7		|_|_|_|_|_|_|_|_|

SOLICITED DIARRHEA SYMPTOM If the symptom continues After 7 days

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 axillary temperature every day. Please take temperature in the evening. 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 continue after 7 day, please continue to assess the following Symptoms until the end of the diarrhea.
(*)If not already collected during the period from D0-D7, please collect stools samples in case of diarrhea leading to medical intervention.

SOLICITED DIARRHEA SYMPTOMS	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__	Date __/__
Axillary Temperature → °C:	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _
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

Stool collection date: |__|__| |__|__| |__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__| |__|__|__|__| hour: |__|__| min: |__|__|

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200|__||__|__| |__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ……..……..…… ☎: ……..……..……

Protocol	DIARY CARD	DOSE 1	Subject number
107625 (Rota-056)	OTHER GENERAL SYMPTOMS AND MEDICATION		|_|_|_|_|_|_|_|_|

Diary Card Template CRF Version 12.4, May 14 2007

UNSOLICITED SYMPTOMS Up to 30 day from vaccination day

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).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis Symptoms) Please give detail below	Intensity 1.Mild 2Moderate 3.Severe	Start date Year month day	End date or check box if continuing Year month day	Continuing
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐

MEDICATION	Please fill in below if any medication has been taken from the vaccination day till 30 days post vaccination					
Trade/Generic name (excluding rehydration)	Reason	Route	Total Daily Dose	Start date Year month day	End date or check box if continuing Year month day	Continuing
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐

☐MEDICAL ATTENTION☐
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |200|_||_|_||_|_|

YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

PLEASE INFORM: ………………………………………… ☎: ……………………………………………………………

Diary Card Template CRF Version 12.4, May 14 2007

Protocol	DIARY CARD	DOSE 2	Subject number
107625 **(Rota-056)**	OTHER GENERAL SYMPTOMS AND MEDICATION		|__|__|__|__|__|__|

UNSOLICITED SYMPTOMS Up to 30 day from vaccination day

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).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis Symptoms) Please give detail below	Intensity 1.Mild 2Moderate 3.Severe	Start date Year month day	End date or check box if continuing Year month day	Continuing
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐
	|__|	200|_||_|_||_|_|	200|_||_|_||_|_|	☐

MEDICATION	Please fill in below if any medication has been taken taken from the vaccination day till 30 days post vaccination					
Trade/Generic name (excluding rehydration)	Reason	Route	Total Daily Dose	Start date Year month day	End date or check box if continuing Year month day	Continuing
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐
				200|_||_|_||_|_|	200|_||_|_||_|_|	☐

☐ **MEDICAL ATTENTION** ☐
- ☐ Hospitalization
- ☐ Emergency room
- ☐ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON 200\|_\|\|_\|_\|\|_\|_\|

YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION

PLEASE INFORM: ………………………………………… ☎: ………………………………………………………

Diary Card Template CRF Version 12.4, May 14 2007

Protocol	DIARY CARD		Subject number
107625 (Rota-056)	GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION	DOSE 1	|__|__|__|__|__|__|__|

GASTROENTERITIS EPISODE□Diarrhea which appears newly after 7 day post vaccination□

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 axillary temperature every day. Please take temperature in the evening. 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 leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

EPISODE No.:

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Axillary temperature → °C:	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _	__ . _
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

Stool collection date: |__|__| |__|__| |__|__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__| |__|__| |__|__|__|__| hour: |__|__| min: |__|__|

□MEDICATION FOR DIARRHEA□ **□MEDICAL ATTENTION□**

- □ Oral rehydration
- □ IV rehydration
- □ Oral and IV rehydration
- □ Other, please specify: _____
- □ Hospitalization
- □ Emergency room
- □ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |200|__||__|__|__|__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: …… ☎: ……

Diary Card Template CRF Version 12.4, May 14 2007

Protocol	DIARY CARD		Subject number
107625 (Rota-056)	GASTROENTERITIS EPISODES LEADING TO A MEDICAL INTERVENTION	DOSE 2	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE□Diarrhea which appears newly after 7 day□

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 axillary temperature every day. Please take temperature in the evening. 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 leading to medical intervention.
Please record the following □MEDICATION FOR DIARRHEA□ and □MEDICAL ATTENTION□.

EPISODE No.:

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C:	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
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

Stool collection date: |__|__||__|__||__|__|__| hour: |__|__| min: |__|__|
Stool collection date: |__|__||__|__||__|__|__| hour: |__|__| min: |__|__|

□MEDICATION FOR DIARRHEA□ **□MEDICAL ATTENTION□**

- □ Oral rehydration
- □ IV rehydration
- □ Oral and IV rehydration
- □ Other, please specify: _____
- □ Hospitalization
- □ Emergency room
- □ Medical Personnel

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |200|__||__|__||__|__|
YOUR CHILD SEEMS THAT MIGHT BE A SERIOUS ILLNESS OR CASE OF HOSPITALIZATION
PLEASE INFORM: ……..…… ☎: ……..……

Diary Card Template CRF Version 12.4, May 14 2007

List of Independent Ethics Committees /Institutional Review Boards

Centre Number(s) *	Ethics Review Body	Location
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone: [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone. [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
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[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]
[redacted]	[redacted]	[redacted] Japan Phone [redacted]

* GSK Biologicals assigned centre number, check with GSM/Study Manager

Representative written information for patient and sample consent forms

Protocol No.: 107625 (Rota-056)
Version 2

Study title: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV.
Company name: GlaxoSmithKline Biologicals KK

Subject identification: _____

HRV Vaccine

Informed Consent Form (Sample)

Written explanation and consent statement for the parent(s)/guardians of the subjects requested to participate in the clinical study of HRV vaccine

Date of Preparation: March 30, 2007

Date of Revision: May 07, 2007

To Parent(s)/Guardians

Human Rotavirus (HRV) vaccine is a vaccine under development by GlaxoSmithKline K.K. It is expected to prevent infection with rotavirus which causes rotavirus gastroenteritis. It has been already approved in more than 60 countries in the world and has been administered to more than one million infants and young children.

The most common cause of diarrhoeal illness in infants and young children is a virus called "rotavirus", which causes gastroenteritis called "rotavirus gastroenteritis (GE)", and most of the children between 6 and 24 months of age are affected.

The most frequently observed symptom of rotavirus disease (or gastroenteritis) is diarrhoea ("white watery stool" such as the water after washing rice) associated with pain and vomiting. This white watery stools may occur for up to ten stools per day and may last from 3 to 9 days. Other symptoms such as fever and abdominal pain may also occur. Diarrhoea 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 infants and young children in developed countries and is a leading cause of death in poorer countries.

As of 15 July 2005, around 89,240 infants have been enrolled in clinical trials with GSK Biologicals' freeze-dried HRV Vaccine. It was confirmed from the study results that "antibodies" (substances in the blood that fight rotavirus infections) were produced in infants and young children by administration of the HRV Vaccine (oral ingestion of the vaccine). Administration of the HRV Vaccine also decreased the occurrence of rotavirus gastroenteritis during the two years after vaccination in Finland and Latin America. The HRV Vaccine also decreases occurrence of severe rotavirus diarrhea in infants and reduces hospitalisation due to rotavirus disease.

Explanation of study participation is to be originally given to a person who is going to participate in the study but the explanation here is to be given to parent(s)/guardians instead of subjects because this study is performed in infants and young children.

Please take time to think before you decide to have your child/ward participate in this study. Immediate reply is not necessary. Please do not hesitate to ask any question. You may also want to bring this document back home and discuss with your family, friends, relatives, etc. Once you read these explanatory documents and you decide to have your child/ward participate in the study, you will be asked to fill in the form (for informed consent) on the last page with dates and your signature or seal.

However, please inform us if your child/ward participated in other study within the past 30 days or have plans to do so.

Please do not leak the information relating to clinical trial to other people because the information and documents that you get with a clinical trial are the confidential information that GSK owns. But it shall not be limited that you talk with your friend and family about this clinical trial as well as doctor to consult about your health control.

1. What is a clinical study?

Currently, various kinds of vaccines and drugs are used and they all have been approved by the Ministry of Health, Labour and Welfare for their use. In order to obtain approval, the results of studies investigating "whether the drug or vaccine has protective effect", "whether the drug or

vaccine is effective", "whether the drug or vaccine is safe", "whether the drug or vaccine is superior to the currently used drugs or vaccines" should be submitted for examination. Among these studies (researches), those conducted in humans are called "Clinical Study". Vaccines or drugs examined in clinical studies are called "Study Vaccine" or "Study Drug".

In the process of development, the effectiveness and safety of a vaccine or drug are first investigated in animals, and then the safety in healthy humans is evaluated by investigating the amount of the drug in blood and urine, etc. After that, some studies are necessary; the vaccine is used in healthy humans to examine whether it prevents the target disease and its safety or the drug is used actually in patients to examine whether the drug is safe and effective.

Clinical studies are therefore necessary steps to create better vaccines to treat the patients to prevent diseases or suffering from diseases.

The procedures and contents of a clinical study are discussed to protect the participants' rights by the Institutional Review Board and the study is started after the approval is obtained. This clinical study has been already discussed and approved in such a manner by the Institutional Review Board.

Institutional Review Board (IRB)

The Institutional Review Board below reviewed and discussed the appropriateness of performing this clinical study.

Type and address of IRB	Contents of review/discussion
IRB of OO Hospital	*Review of the study plan from scientific and ethical aspects*
Name of a technical IRB	*Review of technical items related to OO*
Name of a third party IRB	*Review of the study plan from scientific and ethical aspects*

Please ask when you have a question about IRB (about management and activity of IRB)

2. Why is this clinical study performed?

Since there is no effective treatment for rotavirus gastroenteritis and only the symptomatic therapy (treatment for making the symptom milder) is available, vaccination is the best way to prevent rotavirus gastroenteritis.

GlaxoSmithKline K.K. has developed a new rotavirus vaccine called "HRV Vaccine" based on human rotavirus. The HRV Vaccine is a weakened live vaccine (rotavirus was weakened in toxicity and processed to produce only the antibodies for rotavirus). When a child is vaccinated, the child is expected to develop antibodies (substance in the blood that fights infection) so that only a mild infection with few or no symptoms manifests even if he/she is infected with rotavirus.

This clinical study is performed to investigate the protective effect of the HRV Vaccine against rotavirus gastroenteritis and safety in Japanese infants.

3. What does this study involve?

The study is planned to involve a total of 765 Japanese infants aged 6 to 14 weeks (42 to 104 days after birth). Either of the two types of vaccine, HRV Vaccine and Placebo (product that looks like the real vaccine, but does not contain any active ingredient i.e. virus), will be administered orally. The HRV Vaccine and Placebo are assigned at a ratio of 2:1 (the HRV Vaccine will be given with a probability of 2 out of 3 infants and Placebo to 1 out of 3 infants). Whether your child/ward is assigned to the HRV Vaccine Group or Placebo Group is not known to the physician in charge or you so that the protective effect and side effects of the HRV Vaccine can be objectively evaluated.

Subjects in the HRV Vaccine Group and the Placebo Group will receive two oral doses (the study vaccine is taken orally) of the HRV Vaccine or Placebo at an interval of one month.

All infants participating in this study can receive routine childhood vaccines like DTPa (diphtheria, tetanus toxoids, and pertusis) and HBV (hepatitis B virus vaccine). Other vaccines can be administered according to the Japanese immunisation schedule.

There are a total of five scheduled visits during the study period (until your child/ward becomes 2 years old). You will determine the dates and procedures of visits by consulting the sub-investigator or study nurse so that they do not fall outside the predetermined schedule.

<In order to be included in the study, the following requirements must be met>

- Parent(s)/guardian of the child/ward have given written informed consent.
- The child/ward is aged between 6 and 14 weeks at the time of first vaccination and was born between a gestation period of 36 and 42 weeks inclusive (either boy or girl).
- The child/ward has been confirmed to be healthy before the start of the study by medical history and examination
- Parent(s)/guardians must comply with the requirements of schedule and notes on this Informed Consent Form.

<**Actual procedures and contents of this study are summarised below**>

- Your child/ward will make a total of 5 visits as follows: first vaccination (Visit 1), 1 month after the first vaccination, 2 months after the first vaccination, at the age of 1 year, and at the age of 2 years. During the two years, you will be contacted periodically (at least every 2 weeks) by e-mail, by telephone or by other means to ask the health state of your child/ward.
- Your child/ward will be given a total of two oral vaccinations at the first vaccination (Visit 1) and 1 month later. After each vaccination, you will stay at the study centre for at least 30 minutes to make sure your child/ward is feeling okay before going home.
- Before administration of the vaccine, your child/ward's body temperature will be measured.
- "Diary Card (Solicited symptoms)" "Diary Card (Follow-up of solicited diarrhoea symptoms ongoing after Day 7)", "Diary Card (Other general symptoms and medication)" and "Diary Card (Gastroenteritis episodes)" will be provided to you to record the health state of your child/ward after administration of the study vaccine. Please record the health state of your child/ward on these diary cards and bring them at the next visit.

Diary Card (Solicited symptoms)

Any specific symptom (those listed below) which might occur on the day of vaccination and for the following 7 days (8 days in total):

- Fever (body temperature), fussiness/irritability, loss of appetite, cough /runny nose, vomiting, diarrhoea

Note: If diarrhoea continues after Day 7, please record the end of the symptoms in "Diary Card (Follow-up of solicited diarrhoea symptoms ongoing after Day 7)"

Diary Card (Other general symptoms and medication)

Any symptom (listed below) which might occur on the day of vaccination and during the following 30 days (in total 31 days after the vaccination)

- All symptoms (all unusual symptoms excluding those already recorded in the Diary card for solicited symptoms.

Diary Card (Gastroenteritis Episodes)

From 8 days after vaccination to the end of study: Occurrence of Diarrhoea leading to medical intervention for your child/ward during this period should be recorded.

- If you agree that your child is part of the subset of 60 subjects who will give blood sample, 1 ml (about one teaspoonful) of blood will be collected from your child/ward at the scheduled two visits (at the first vaccination and 2 month later). The purpose of the blood sample collection is to evaluate the immune responses (i.e. production of antibodies) to the HRV Vaccine that your child/ward may receive. Blood samples will not be used for any other purpose than investigation of the HRV Vaccine.
- At each visit, a physical examination will be performed and the feeding practices of your child will be recorded.
- 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.
  - Intussusception: Serious disease with telescoping of one portion of the intestine into another: symptoms consistent with intussusception are, severe colicky abdominal pain (the child may cry hard by pulling his/her legs up to the trunk), quite normal activities between episodes, persistent vomiting, strawberry jam-like stools, abdominal bloating (abdominal distension), and high fever (up to 41°C in some cases).
- You should also collect a stool sample from your child/ward during occurrence of diarrhoea (Passage of three or more looser than normal stools within a day) leading to medical intervention. Stool samples should be collected in a container provided by the institution as soon as possible (not later than 7 days after the occurrence of diarrhoea (diaper with stool is acceptable if it is difficult to collect a stool sample). If diarrhoea recurs after 5 days after disappearance of the symptom, it should be considered as a separate episode and you should take a stool sample again.
- You will be asked to report the following information about your child/ward:
  - Use of any medication or other vaccine/placebo during the study period.

– Symptoms and diagnosis, if your child/ward receives examination/treatment at other department or medical institution

- Note: You should contact the physician in charge or other study nurse immediately should your child/ward have any signs or symptoms you think may be serious, or if your child/ward is hospitalised during the study period.

– **List of investigation items during the study –**

Timing of Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	6-14 weeks after birth	1 month later	2 month later	At the age of 1 year	At the age of 2 years
Medical examination	●	●	●	●	●
Body temperature before vaccination	●	●			
Vaccination	●	●			
Submission/return of Diary Card (Solicited symptoms)	●	●	●		
Diary Card (Follow-up of solicited diarrhoea symptoms ongoing after Day 7)	●	●	●		
Submission/return of Diary Card (Other general symptoms and medication)	●	●	●		
Collection of GE stool samples*	●	●	●	●	●
Submission/return of Daily Card (Gastroenteritis episodes)	●	●	●	●	●
Blood collection**	●		●		

* Stools samples are to collected it when your child/ward has diarrhoea (Passage of three or more looser than normal stools within a day) leading to medical intervention

**Blood samples will be taken from your child/ward only if you agree to be part of the immuno subset.

4. How long is the duration of participation in the study?

The participation of your child/ward in the study is about 22 months, starting from the first dose of HRV vaccine/Placebo until your child/ward becomes 2 years of age.

5. How many other subjects are there in the study?

This study will involve a total of approximately 765 male or female infants in multiple centres in Japan.

6. Does your child/ward have to participate in the study? Does your child/ward have to stay in the study?

You may refuse your child's/ward's participation in this study, or once in the study you may decide to discontinue participation at any time. Your decision to not let your child/ward take part in the study or to stop participating in the study will not affect your child's/ward's current or future medical care, or any benefits to which your child/ward may otherwise be entitled. However, the sponsor of this study, GlaxoSmithKline K.K., will store and use the information obtained in this study without disposing it even if your child/ward discontinues participation in the study.

Study participation may be discontinued in the cases described below. In these cases, you will be informed of the reason for discontinuation.

- When the parent(s)/guardian wishes study discontinuation.

- When it is found out that your child/ward should not participate in the study after the study initiation.
- When the study has reached the required number of subjects.
- When your child's/ward's participation in the study is judged to be difficult due to side effects.
- When discontinuation of your participation is judged necessary by the physician in charge upon the medical judgment.
- When your child/ward changes his hospital and cannot make a hospital visit any longer.
- When the study itself is discontinued due to the sponsor's own reason.

When new information that may affect your willingness to let your child/ward stay in the study becomes available, we will tell you as soon as possible about the information. You will be asked to determine whether or not to continue participation in the study.

7. What are the foreseeable benefits for taking part in the study? What are the expected side effects?

<Foreseeable benefits>

When your child/ward is vaccinated with the HRV Vaccine, there may not be gastroenteritis symptoms such as diarrhoea and vomiting or the symptoms may be mild even if he/she is infected with rotavirus and your child/ward will be protected against rotavirus gastroenteritis. When a Placebo is vaccinated, there is no foreseeable benefit.

<Side effects observed so far>

The HRV Vaccine has been studied in overseas research studies in which approximately 40,200 infants and young children received the said vaccine. Most of the adverse experiences observed with the HRV Vaccine were mild (Table below) and the incidence of the adverse experiences caused by the HRV Vaccine was similar to that of placebo.

≥ 10%	≥ 0.1% and < 1%	≥ 0.01% and < 0.1%	< 0.01%
Irritability and loss of appetite	Fever, fatigue, diarrhoea, vomiting, flatulence (gas), abdominal pain, and regurgitation of food	Crying, sleep disorder, somnolence (sleeping longer than usual, or always looking drowsy), constipation,	upper respiratory tract infection, hoarseness, rhinorrhoea, dermatitis, rash, and muscle cramp (twitching of the muscles)

It was reported in an overseas study that the rate of occurrence of intussusception was increased with a different HRV vaccine (other than GSK Biologicals vaccine) which was used in the United States in 1998. In a large safety trial (involving about 63,200 infants and young children), the results have shown that the HRV Vaccine being tested in this study does not increase the possibility of causing intussusception compared with placebo (HRV Vaccine is not likely to cause intussusception). As with any experimental vaccine, unexpected serious adverse experiences, including allergic reactions to the vaccine, may occur. All the medical equipment necessary to treat any serious reactions to the study vaccine will be available at the investigation site.

If your child is part of the immunogenicity subset, there may be momentary, mild discomfort and bruising of the skin where the needle is inserted to draw blood. The amount of blood to be taken is

so small that it will not cause any general symptoms or anaemia (a condition with insufficient red blood cells).

8. Are there alternative products or treatment?

There is no licensed rotavirus vaccine or drug currently available in Japan. Gastroenteritis caused by rotavirus is treated with oral rehydration solutions to prevent dehydration due to diarrhoea. Intravenous fluid replacement may be necessary when it is difficult to orally take water or dehydration becomes worse even if a patient can take water. Usually no treatment is performed to improve vomiting or diarrhoea caused by rotavirus gastroenteritis.

9. Who will make payment for participation in the study?

There will be no charge for study-related doctor visits, examinations and laboratory tests.

When you allow your child/ward to participate in this study, _____ yen will be paid to you for each visit to reimburse the cost of traveling to and from study visits and communication costs related to the study.

10. Who should you contact to answer any questions on the study?

If you have any questions concerning this study, please contact the physician in charge (investigator, subinvestigator) or other study nurse at the telephone number below.

Hospital:

		Name (affiliation/title)	Contact (telephone number)
Physicians in charge	Investigator	(Director, pediatrics) OO OO (Chief physician, pediatrics)	OO-OOOO-OOOO
	Sub-investigator	OO OO (physician, pediatrics) OO OO (physician, pediatrics) OO OO (physician, pediatrics)	
Study nurse		OO OO (study coordinator) OO OO (study coordinator) OO OO (study coordinator)	

11. In the event if your child/ward is injured in the study, what compensation will be available?

If you believe your child/ward has sustained a research-related injury such as side effects during or after completion of the study, you should contact the physician in charge or other study nurse immediately. Appropriate examination and treatment will be given. The expenses required for treatment and other damages will be appropriately compensated if the cause of injury is related to this study. However, compensation may be reduced or no compensation will be made if the injury is caused by your failure to observe the instructions of the physician in charge or your false report.

12. Who will have access to medical and personal information about your child/ward that is collected in this study? In that case, is the personal information protected?

If you decide to allow your child/ward to 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 staff who see this information at the site will keep it confidential.

The study site will also transfer to GSK some of the information it collects, in a coded form. The information transferred will not include your child/ward's name, initials, address, or other direct identifiers. It will be assigned a code number that only the site can connect back to your child's/ward's name.

Your permission to the study doctor and staff to use this information or share it with GSK and others as described below for the study doesn't automatically end at a particular time.

Medical information about your child/ward may be produced as part of the research or study procedures. If at the time of the study, this information is known to be relevant to your child's/ward's medical care it will be given to the study doctor who will be encouraged to share it with you or your child's/ward's doctor. While your child/ward is in the study, however, the study site will not share certain new medical information about your child/ward that is created as part of the study (such as whether or not your child/ward is getting study drug, or the results of certain tests) unless the study doctor decides it is medically important to do so. This is done to stop the study results from being distorted. Once the study is over, your child/ward will be given access to medical information about your child/ward that you are entitled to see. You will be told if any of this medical information requires confirmation using a clinical test. This is important because some research results are for research purposes and may have only limited relevance for clinical diagnosis or treatment. At any time, you may ask your study doctor to let you see your child's/ward's personal information, e.g. name and address and to correct it if necessary.

13. What will GlaxoSmithKline do with the information it gets?

GSK may use the information obtained in the clinical study (the subject number will be used in place of your child's/ward's name) in the following manner:

- By placing it under strict storage. The information will be analysed to find out what this study is telling us.

- By sharing it with regulatory authorities that approve new medicines, or with groups that check that research is done properly
- By publishing the results of the study. The study results obtained from your child/ward may be used for approval application or published in science journals. In such cases, your child's/ward's name will be replaced by a symbol or number so that your child's/ward's personal information can be secured.
- By sharing it as part of research with other companies or universities and with other GlaxoSmithKline offices in this country and in other countries for the purpose of further understanding or developing this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- By using it to plan new studies or other types of research or other medical purposes related to the development of the vaccine.

14. What will happen to the stool and blood samples obtained in this study?

The samples of diarrhoeal stool or blood (only when prior informed consent is obtained to sample the blood of your child/ward) will be collected in this study to evaluate the immunogenicity and efficacy of the study vaccine. The subject number instead of the name of your child/ward will be attached to the collected samples to protect the privacy of your child/ward and the collected samples will be transferred to GlaxoSmithKline K.K. or to other testing institutions working with GlaxoSmithKline K.K. and then tested there.

By agreeing to take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:

- Testing to measure the immune response (e.g. amount of antibodies) and efficacy of the vaccine your child/ward received during the Study.
- Testing to assure that the results from your child's/ward's sample are of good quality, for improvements of those tests.
- Collected samples will be stored for up to 15 years.

15. How is GlaxoSmithKline involved?

The study is conducted upon GSK request. The institution is paid to conduct this research study by GSK.

16. Is there any requirement to be observed by participating in the study?

Please make sure to observe the items below because they are necessary to maintain the health of your child/ward during the study -

- Please let the physician in charge or other study nurse know immediately if you feel something different in your child's/ward's body or experience any unusual events in daily life such as fracture and fall which are generally considered unlikely to be related to the study after stating the study vaccine.
- Please let the physician in charge or other study nurse know as soon as possible when you want to discontinue your child's/ward's participation in the study after starting the study vaccine.

- In case that you take your child/ward to visit other department or physician after starting the study vaccine, please let the physician know your child's/ward's participation in the study. Also, please let the physician in charge know such visit.
- Please contact the physician in charge or other study nurse when your child/ward occurrence of diarrhoea (Passage of three or more looser than normal stools within a day) leading to medical intervention.
- Please make accurate entries on the Diary Card you received according to the instructions of the physician in charge or other study nurse because they are important information for finding out the reaction to the study vaccine.
- Please contact us in advance if you cannot make a visit on the day informed by the physician in charge or other study nurse.

Please put your signature on next page if you agree on your child's/ward's participation in the study after reading the descriptions on this explanatory document.

Protocol No.: 107625 (Rota-056)
Version 2
Subject identification:_____

Consent statement

A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination, in healthy infants previously uninfected with HRV.

I, (Printed name of Subject's parents/guardians)

- confirm that I have read the written information (or have had the information read to me) for study 107625 (Rota-056) dated 07 May 2007, total of 13 pages, and the study procedures have been explained to me by study staff during the consent process for this study.
- 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 taking part in this study.

Tick as appropriate (this decision will not affect your ability to enter the study):

I agree that my child's/ward's primary health care physician will be notified of my child's/ward's participation in this study. **Yes** **No**

I agree to be part of the blood sample subset: **Yes** **No**

I agree to let my child/ward to take part in this study.

I received the copy of this consent statement.

Signature of Legal Representative _____ **Date:** _____

Relationship _____

Signature of investigator _____ **Date:** _____

Date of explanation given by Investigator

Signature of study nurse _____ **Date:** _____

Date of explanation given by study nurse

List of investigators and other important participants in the study, contact information and number and distribution of subjects

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* GSK Biologicals' assigned center number
As of 30Jun 2009

Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

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 annex study report, including appendices

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study: 107625 (Rota-056) Development Phase: III

I have read this annex 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: _____

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GlaxoSmithKline Biologicals
Global Clinical Research and Development

Sponsor Signatory Approval Page

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Study: 107625 (Rota-056) Development Phase: III

I have read this annex 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] M.B.B.S

Title of Sponsor Signatory: Director, Rotavirus vaccines
Global Clinical Research and Development
GlaxoSmithKline Biologicals

Signature: _____

Date: _____

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GlaxoSmithKline Biologicals
Global Clinical Research and Development

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Study: 107625 (Rota-056) Development Phase: III

I have read this annex report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Dr. [redacted]

Title of Sponsor Signatory: Deputy Director, Clinical Development, GlaxoSmithKline K.K.

Signature: _____

Date: _____

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ab948d78d992e0dee6aa2b53bb1031e3 1.0 26/04/2010 12:44:49 - -
18838a9d79734bed9cae2df4b0985818 1.0 26/04/2010 12:42:46 - -
36bbfb89252b3f1e429164fc2fbd9d64 1.0 26/04/2010 12:43:56 - -
2cdf3276f92181e386f1ad7dcd891c8c 1.0 26/04/2010 15:11:36 - -
44fa694b73f25c006a7252c671144b44 1.0 26/04/2010 12:43:21 - -
5f1c35fc52c04e946b406627bd7fac67 1.0 26/04/2010 12:41:12 - -
5d4cf41150398204f0ba13b80c64a5ab 1.1 28/04/2010 16:30:36 - -
f6269e93be33a5bb85e39a51f88c38aa 1.0 26/04/2010 12:49:38 - -
fb3229ca4b3162860266db1548cefefe 1.0 26/04/2010 12:46:35 - -
a6dee950f10c56865248a85eaa8ab711 1.0 26/04/2010 12:42:11 - -
2896a247e135ca8c2ca6b2f755987fb9 1.0 26/04/2010 12:40:14 - -
26badc593ee60d5d1feabb2a8fd8392b 1.1 28/04/2010 16:16:28 - -
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Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable

Randomisation list

CDMCI\ RDE\ ENABLE

Randomisation list

ROTA-056 (A.01MAR2010)

Subjects from Group: HRV - HRV

Trt.	Bl.	Repl.	Trt.	Bl.	Repl.	Trt.	Bl.	Repl.	Trt.	Bl.	Repl.	Trt.	Bl.	Repl.	Trt.	Bl.	Repl.	Trt.	Bl.	Repl.
No	nb	flag	No	nb	flag	No	nb	flag	No	nb	flag	No	nb	flag	No	nb	flag	No	nb	flag
[redacted]	159	Y	[redacted]	168	Y	[redacted]	78	Y	[redacted]	187	Y	[redacted]	9		[redacted]	18		[redacted]	28	
	159	Y		168	Y		78	Y		187	Y		9			18			28	
	159	Y		169	Y		78	Y		188	Y		9			19			28	
	159	Y		169	Y		78	Y		188	Y		9			19			28	
	160	Y		169	Y		79	Y		188	Y		10			19			29	
	160	Y		169	Y		79	Y		188	Y		10			19			29	
	160	Y		170	Y		79	Y		1			10			20			29	
	160	Y		170	Y		79	Y		1			10			20			29	
	161	Y		170	Y		80	Y		1			11			20			30	
	161	Y		170	Y		80	Y		1			11			20			30	
	161	Y		171	Y		80	Y		2			11			21			30	
	161	Y		171	Y		80	Y		2			11			21			30	
	162	Y		171	Y		81	Y		2			12			21			31	
	162	Y		171	Y		81	Y		2			12			21			31	
	162	Y		172	Y		81	Y		3			12			22			31	
	162	Y		172	Y		81	Y		3			12			22			31	
	163	Y		172	Y		82	Y		3			13			22			32	
	163	Y		172	Y		82	Y		3			13			22			32	
	163	Y		173	Y		82	Y		4			13			23			32	
	163	Y		173	Y		82	Y		4			13			23			32	
	164	Y		173	Y		83	Y		4			14			23			33	
	164	Y		173	Y		83	Y		4			14			23			33	
	164	Y		174	Y		83	Y		5			14			24			33	
	164	Y		174	Y		83	Y		5			14			24			33	
	165	Y		174	Y		84	Y		5			15			24			34	
	165	Y		174	Y		84	Y		5			15			24			34	
	165	Y		175	Y		84	Y		6			15			25			34	
	165	Y		175	Y		84	Y		6			15			25			34	
	166	Y		175	Y		85	Y		6			16			25			35	
	166	Y		175	Y		85	Y		6			16			25			35	
	166	Y		176	Y		85	Y		7			16			26			35	
	166	Y		176	Y		85	Y		7			16			26			35	
	167	Y		176	Y		86	Y		7			17			26			36	
	167	Y		176	Y		86	Y		7			17			26			36	
	167	Y		177	Y		86	Y		8			17			27			36	
	167	Y		177	Y		86	Y		8			17			27			36	
	168	Y		177	Y		87	Y		8			18			27			37	
	168	Y		177	Y		87	Y		8			18			27			37	

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Randomisation list

ROTA-056 (A.01MAR2010)

Subjects from Group : HRV - HRV

Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
[redacted]	47	
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
[redacted]	94	
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Randomisation list

ROTA-056 (A.01MAR2010)

Subjects from Group : HRV - HRV

Trt. No	Bl. nb	Repl. flag
[redacted]	104	
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Trt. No	Bl. nb	Repl. flag
[redacted]	113	
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Trt. No	Bl. nb	Repl. flag
[redacted]	123	
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Trt. No	Bl. nb	Repl. flag
[redacted]	132	
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Trt. No	Bl. nb	Repl. flag
[redacted]	142	
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Trt. No	Bl. nb	Repl. flag
[redacted]	151	
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Randomisation list

ROTA-056 (A.01MAR2010)

Subjects from Group : Placebo - Placebo

Trt. No	Bl. nb	Repl. flag
[redacted]	159	Y
	159	Y
	160	Y
	160	Y
	161	Y
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	162	Y
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	163	Y
	163	Y
	164	Y
	164	Y
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	167	Y
	168	Y
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	172	Y
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Trt. No	Bl. nb	Repl. flag
[redacted]	178	Y
	178	Y
	179	Y
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	182	Y
	182	Y
	183	Y
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Trt. No	Bl. nb	Repl. flag
[redacted]	9	
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
[redacted]	66	
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Trt. No	Bl. nb	Repl. flag
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CDMCI\ RDE\ ENABLE

Randomisation list

ROTA-056 (A.01MAR2010)

Subjects from Group : Placebo - Placebo

Trt. No	Bl. nb	Repl. flag
[redacted]	104	
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Trt. No	Bl. nb	Repl. flag
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Trt. No	Bl. nb	Repl. flag
[redacted]	142	
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Audit Certificates

Audit Certificate

During the conduct and reporting of this study, the following independent GCP* audit was performed in Japan by GlaxoSmithKline K.K. Regulatory Compliance Department.

Clinical study drug code: 444563

Protocol number: 107625(Rota-056)

Study title: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study period: 19th June 2007 (FSFV) – ongoing

Audit Type	Audit date	Issue date of audit report	Referred SOP
Protocol (Informed Consent Form)	4th-10th Apr. 2007	9th May 2007	SOP/GSK/CC/003/03
Investigator site			
[redacted]			
In-house audit	6thAug.-8thSep.2008	28th Oct. 2008	SOP/GSK/RCD/005/01
On-site audit	9th - 10th Sep. 2008		
Documents/records audit	8th Sep. 2008		

Name [redacted]

Date: Sept. 8, 2009

[redacted]

Department Manager,
Regulatory Compliance Department
Development and Medical Affairs Division
GlaxoSmithKline K.K.

* Ministry of Health and Welfare Ordinance No.28, 1997, and its amendments.

AUDIT CERTIFICATE

Study Number: 107625

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/these study(s), the following independent audits were performed by or on behalf of GlaxoSmithKline.

Study Number	Type	Conducted by	Centre number	Country	Audit Date
107625	Investigator site	CQA	[redacted]	Japan	31 March - 3 April 2008

Clinical Quality Assurance 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, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

Name: [redacted] **Date:** 11 September 2009

Role: Manager

Clinical Quality Assurance
GlaxoSmithKline Research and Development

Documentation of statistical methods

Refer to the Study 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

This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.

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 activities
	3	: 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****.*

Case report forms (CRFs /eCRFs)

This appendix is provided as 1 separate PDF file

Document Name	Checksum	Version	Created on
ROTA-056 (107625) CRFs for SAEs	19c7b0b95e9ff7baec96c55472f68223	1.0	27/04/2010

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
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 annex study report, including appendices

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multicentre study in Japan to assess the efficacy, safety, reactogenicity and immunogenicity of the lyophilised formulation of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine, given as a two-dose primary vaccination course, in healthy infants previously uninfected with HRV.

Study: 107625 (Rota-056) Development Phase: III

I have read this annex 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] M.B.B.S

Title of Sponsor Signatory: Director, Rotavirus vaccines
Global Clinical Research and Development
GlaxoSmithKline Biologicals

Signature: [redacted]

Date: 29 Apr 2010

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Study: 107625 (Rota-056) Development Phase: III

I have read this annex report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Dr. [redacted]

Title of Sponsor Signatory: Deputy Director, Clinical Development, GlaxoSmithKline K.K.

Signature: [redacted]

Date: 21. Apr. 2010

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