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- *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*

GlaxoSmithKline Biologicals

Study title

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, safety and immunogenicity of two or three doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine Expanded Program of Immunisation (EPI) vaccinations in healthy infants.

Clinical Study Report for Study 102248 (Rota-037)
(Development Phase III)

Indication Studied: Immunization against rotavirus disease in healthy infants aged 5 to 10 weeks at the time of the first dose.

Study initiation date:	24 October 2005
Study completion date:	27 June 2008
Date of report:	16 March 2009
Earlier Study Reports:	Interim Report dated 26 March 2008: Interim analysis for efficacy against any rotavirus gastroenteritis (RV GE) and severe RV GE in the Cohorts 1 and 2 in South Africa for the period starting from 2 weeks after the last dose of the HRV vaccine or placebo up to Visit 6 (or at the last contact if Visit 6 was not performed) or 31 August 2007 whichever was the earliest.
Report Scope:	This report presents the efficacy, immunogenicity and safety results for all cohorts for the period starting from 2 weeks after the last dose of the HRV vaccine or placebo up to Visit 6 (i.e. end of the first efficacy period).

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[redacted] M.D,
Director, Rotavirus Clinical Trials,
Program for Appropriate Technology in Health

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

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SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** HRV Vaccine **Name of active substance:** RIX4414 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, multi-centre study to assess the efficacy, safety and immunogenicity of two or three doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine Expanded Program of Immunisation (EPI) vaccinations in healthy infants.

Principal investigator: The study was conducted by 10 principle investigators. Dr. [redacted] was the national coordinating investigator in South Africa and Dr. [redacted] was the principle investigator in Malawi. Dr. [redacted] and Dr. [redacted] reviewed and approved this study report on behalf of all investigators.

Study centres: The study was conducted at multiple sites in South Africa and Malawi.

Publication (reference): Not published as of 16 March 2009.

Study period: Study initiation date: 24 October 2005 Study completion date: 27 June 2008	**Clinical phase: III**

Objectives: The study objectives considered for analyses presented in this study report are listed below.

Primary:

- To determine if the GSK Biologicals' HRV vaccine (HRV pooled group) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of the HRV vaccine or the placebo up to Visit 6.

Criteria: The primary objective will be reached if the lower limit of the 95% CI on vaccine efficacy is >0%.

Secondary:

Efficacy

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

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

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the of HRV vaccine or placebo until Visit 6.
- In South Africa, to assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

Safety

- In all subjects, to assess the safety of two or three doses of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations compared with placebo in terms of AEs leading to drop-out and SAEs during the entire course of the study.

Immunogenicity

- In a subset of subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seropositivity rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after completion of the HRV vaccine course.

Study design: Double-blind, randomised (1:1:1), placebo-controlled study with three parallel groups:

- **HRV 3-Dose group (also referred to as HRV_3D group):** 3 doses of HRV were to be given concomitantly with routine Expanded Program of Immunisation (EPI) vaccines at 6, 10 and 14 weeks of age.
- **HRV 2-Dose group (also referred to as HRV_2D group):** 2 doses of HRV were to be given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose was to be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding).
- **Placebo group:** 3 doses of placebo were to be given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age.

All subjects had a total of five study visits [Visit 1 (i.e. Day 0), Visit 2 (i.e. Month 1), Visit 3 (i.e. Month 2), Visit 4 (i.e. Month 3) and Visit 6 (i.e. at one year of age)]. Subjects who underwent initial Human Immunodeficiency Virus (HIV) testing at Visit 4 had an additional visit [Visit 5 (i.e. Month 4)] to communicate HIV test results to the subject's parents/guardians. Routine EPI schedule vaccines were administered concomitantly with the study vaccine at Visits 1, 2 and 3. Data collection was done using hard copy case report form. This study report contains the efficacy, safety and immunogenicity analyses of all subjects who have completed Visit 6 at one year of age.

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Number of subjects	Total	HRV_2D	HRV_3D	HRV_POOL	Placebo
Enrolled	4941				
Vaccinated (Total vaccinated cohort)	4939	1647	1651	3298	1641
Completed Visit 6	4195	1420	1383	2803	1392
According-to-protocol (ATP) for efficacy	4417	1496	1478	2974	1443
ATP cohort for immunogenicity	3423	1160	1138	2298	1125

Diagnosis and criteria for inclusion: Healthy infants who were 5 to 12 weeks of age at Dose 1 of HRV vaccine/placebo, free of obvious health problems as established by medical history and clinical examination before entering into the study, and with written informed consent obtained from parents or guardians.

Study vaccine, dose, mode of administration, lot no.:
Vaccination schedule /site: Subjects in HRV 3-Dose group were to receive three oral doses and subjects in HRV 2-Dose group were to receive two oral doses of the lyophilised formulation of the HRV vaccine at 6, 10, 14 weeks of age and 10, 14 week of age, respectively.
Vaccine composition /dose /lot number: Each dose (1.3 ml) of GSK Biologicals' HRV vaccine lyophilised formulation 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 80 mg of Calcium carbonate and 0.25% of Xanthane in 1.3 ml of water for injection. Lot numbers [redacted] and [redacted] were used for the HRV lyophilised vaccine. Lot number [redacted] was used for the diluent. In Malawi, lot number [redacted] was used for the HRV lyophilised vaccine and lot number [redacted] 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 three doses of the placebo at 6, 10, 14 weeks of age and subjects in HRV 2-Dose group were to receive one dose of the placebo at 6 weeks of age.
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 numbers [redacted] [redacted] were used for the placebo. The same diluent was used to reconstitute the HRV vaccine and the placebo.

Duration of study: The study duration from Visit 1 to Visit 6 was approximately 10-11 months per subject.

Criteria for evaluation of efficacy:
A GE episode was defined as occurrence of diarrhoea with or without vomiting. A severe GE/ RV GE episode was defined as an episode of GE/RV GE scored ≥11 on the 20-point Vesikari scoring system [Ruuska, 1990]. Diarrhoea was defined as passage of three or more looser than normal stools (loose or watery stools) within a day. Stool samples were tested by Enzyme Linked Immunosorbent Assay (ELISA) for RV detection. All stool samples that were RV positive were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) to determine the serotype. This technique also allowed differentiation between the G1 vaccine virus and the wild-type G1 RV.
Primary endpoint:

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains in pooled HRV groups versus the placebo group during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

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Secondary efficacy endpoints:

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 6.
- In South Africa, occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

Criteria for evaluation of safety: Recording of SAEs during the entire study period. Recording of non-serious adverse events (AEs) leading to subject withdrawal or drop-out.
Secondary safety endpoint:

- For all subjects, occurrence of AEs/SAEs leading to drop-out throughout the entire study period.
- For all subjects, occurrence of SAEs throughout the entire study period.

Criteria for evaluation of immunogenicity:
Blood samples were collected from a subset of subjects at Visit 1 (to measure anti-rotavirus IgA antibodies). Blood samples were collected from all subjects at Visit 4 (to measure anti-rotavirus IgA antibodies).
Secondary immunogenicity endpoints:

- In a subset of subjects, seroconversion rate and Geometric Mean concentration (GMC) to anti-rotavirus IgA antibody at Visit 4.
- In all subjects, seropositivity rate and GMC to anti-rotavirus IgA antibody at Visit 4.

Statistical methods:
Analysis of demography: The mean and standard deviation (SD) of height in cm and weight in kg at Visit 1 and increase in height and weight from Visit 1 to Visits 4 and 6 were calculated per group and overall. The country, racial and gender distributions were presented. The mean, median range and SD of age in weeks at each dose of HRV vaccine or placebo were calculated per group and overall. The median, mean, range and SD of age in months at Visit 6 or at last contact if the study visit was not performed were also calculated per group and overall. HIV status during the study and malnutrition status at Visits 1, 4 and 6 were summarised by group and overall.

Analysis of efficacy: The percentages of subjects with severe RV GE from 2 weeks after Dose 3 up to Visit 6 (P) and group difference was primarily quantified using vaccine efficacy defined as 1- ($P_{\text{pooled HRV group}}$/ P_{placebo}), its exact 95% CI. This primary analysis was complemented by 2-sided fisher exact test and by vaccine efficacy and associated CI derived from a Cox regression model on the time to first event with censoring at Visit 6 for subjects without the event.

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The primary study objective was reached if there was a statistically significant vaccine efficacy: to account for an interim analysis, statistical significant vaccine efficacy at the final analysis had to be based on a 2 sided p-value below 0.038 (O'Brien & Fleming type I error adjusted for the 35 subjects with severe RV GE included in the interim analysis with an interim nominal alpha=0.0155 and the final 136 number of severe RV GE, EAST).
The secondary efficacy endpoints were analysed in a similar way. Futher analyses by country and using an alternative severity scoring systems were conducted.
Finally, the ATP cohort analyses of efficacy were complemented by total vaccinated cohort analysis for:

- RV GE from Dose 1 until Visit 6,
- RV GE from Dose 1 until 2 weeks post-Dose 3,
- RV GE from Dose 1 until Dose 3.

Analysis of safety: The percentage of subjects with SAEs, fatalities and with AEs/SAEs leading to drop out was tabulated by group according to MedDRA classification, with its exact 95% CI. Exploratory analyses for fatality due to "Lower respiratory tract and lung infection" and due to "pneumonia" were performed. Exploratory group comparisons between each and pooled HRV group versus the placebo group were performed using asymptotic 95% CI for the group difference and the associated 2-sided p-value to detect group difference.
Analysis of immunogenicity: For each group, at each time point that a given antigen was measured,

- Seropositivity/seroconversion rates and their exact 95% CI were tabulated.
- Geometric mean concentrations (GMCs) and their 95% CI were calculated.

The asymptotic standardised 95% CI for difference in the percentage of subjects who were seropositive for anti-rotavirus IgA antibody concentrations at Visit 4 between groups (each HRV group versus placebo group, pooled HRV groups versus placebo group and HRV_2D group versus HRV_3D group) was computed.

Summary:
Demography Results: In the ATP cohort for efficacy, the mean age was 6.3 weeks (range: 2 to 11 weeks) at Dose 1 of HRV vaccine/placebo, 11.3 weeks (range: 8 to 21 weeks) at Dose 2 of HRV vaccine/placebo and 16.2 weeks (range: 12 to 26 weeks) at Dose 3 of HRV vaccine/placebo. The mean age at Visit 6 or last contact if Visit 6 was not performed was 11.6 months (range: 3 to 28 months). Majority of the subjects (96.9%) were of African heritage or African American.

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 period from 2 weeks after Dose 3 up to Visit 6 was 7.2 months in both the HRV pooled group and placebo group.

- Significantly fewer subjects in the HRV pooled group reported severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV compared to the placebo group (1.9% versus 4.9%, p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV was 61.2% [95% CI: 44.0%; 73.2%]. The primary efficacy objective of the study was reached.
- Vaccine efficacy against severe RV GE caused by the circulating wild-type RV was 58.7% [95% CI: 35.7%; 74.0%] in the HRV_2D group and 63.7% [95% CI: 42.4%; 77.8%] in the HRV_3D group.

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- Significantly fewer subjects in the HRV pooled group reported any RV GE caused by the circulating wild-type RV compared to the placebo group (5.6% versus 12.1%; p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against any RV GE caused by circulating wild type RV was 53.4% [95% CI: 42.1%; 62.6%].
- The number of subjects with severe RV GE episodes caused by G1 wild type in the HRV pooled group was significantly lesser compared to the placebo group (0.6% versus 1.6%; p-value: 0.002). Vaccine efficacy against severe RV GE caused by G1 wild type was 64.1% [95% CI: 29.9%; 82.0%].
- When considering all isolated non-G1 types (G2, G3, G8, G9 and G12), significantly fewer subjects in the HRV pooled group reported severe RV GE compared to the placebo group (1.3% versus 3.3%; p-value: <0.001). Vaccine efficacy against severe RV GE caused by non-G1 types was 59.7% [95% CI: 37.1%; 74.4%].
- Fewer subjects in the HRV pooled group were hospitalised due to RV GE from 2 weeks post Dose 3 up to Visit 6 (0.5% versus 1.1%; p-value 0.019). Vaccine efficacy against hospitalisation due to RV GE was 57.5% [95% CI: 7.2%; 80.8%].
- All cause severe GE was reported by significantly fewer subjects in the HRV pooled group compared to the placebo group (8.6% versus 12.3%; p-value <0.001). Vaccine efficacy against all cause severe GE was 30.2% [95% CI: 15%; 42.6%].

The total vaccinated cohort was used for the secondary analysis of efficacy from Dose 1 onwards.

Synopsis Table 1: Vaccine efficacy from 2 weeks post Dose 3 up to Visit 6 (ATP cohort for efficacy)

			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 (primary efficacy endpoint)									
HRV_POOL	2974	56	1.9	1.4	2.4	61.2	44.0	73.2	<0.001
Placebo	1443	70	4.9	3.8	6.1	-	-	-	-
Severe RV GE due to G1 wild type									
HRV_POOL	2974	17	0.6	0.3	0.9	64.1	29.9	82.0	0.002
Placebo	1443	23	1.6	1.0	2.4	-	-	-	-
Severe RV GE due to non-G1 types									
HRV_POOL	2974	39	1.3	0.9	1.8	59.7	37.1	74.4	<0.001
Placebo	1443	47	3.3	2.4	4.3	-	-	-	-
Any RV GE due to circulating wild-type RV									
HRV_POOL	2974	167	5.6	4.8	6.5	53.4	42.1	62.6	<0.001
Placebo	1443	174	12.1	10.4	13.9	-	-	-	-
RV GE requiring hospitalisation									
HRV_POOL	2974	14	0.5	0.3	0.8	57.5	7.2	80.8	0.019
Placebo	1443	16	1.1	0.6	1.8	-	-	-	-
All cause severe GE									
HRV_POOL	2974	256	8.6	7.6	9.7	30.2	15.0	42.6	<0.001
Placebo	1443	178	12.3	10.7	14.1	-	-	-	-

N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event; VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

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Synopsis Table 2: Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	30	2.0	1.4	2.9	58.7	35.7	74.0	<0.001
HRV_3D	1478	26	1.8	1.2	2.6	63.7	42.4	77.8	<0.001

N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test; Note: 2 sided Fisher exact test comparing 2 doses versus 3 doses=0.686

Safety Results: The safety analysis was performed only on the total vaccinated cohort.

- The percentage of subjects with at least one symptom leading to drop out was 2.8% in the HRV pooled group (2.8% in the HRV_2D group and 2.7% in the HRV_3D group) and 2.7% in the placebo group.
- From Dose 1 of HRV vaccine up to Visit 6, 126 fatal SAEs were reported in the study (83 subjects (2.5%) in the HRV pooled group and 43 subjects (2.6%) in the placebo group). An additional gastroenteritis fatality with unknown start date of symptom was reported in the placebo group.
- At least one SAE occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 was reported in 9.7% in the HRV pooled group (10.3% in the HRV_2D group and 9.0% in the HRV_3D group) and 11.5% in the placebo group.
- One subject in the HRV_3D group developed Intussception (IS) 78 days after receiving Dose 3 of HRV vaccine. The SAE was assessed by the investigator not to be causally related to vaccination.
- There were 3 subjects in the HRV pooled group with report of at least one SAE assessed as related to vaccination. Acute Otitis Media was reported for 1 subject in the HRV_3D group and Sepsis was reported for 2 subjects in the HRV_3D group.

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

- The seropositivity rate for all subjects (n = 1462) with post-vaccination blood samples at one month post Dose 3 of HRV vaccine/placebo was 63.6% [95% CI: 61.6%; 65.6%] in the HRV pooled group and 23.3% [95% CI: 20.8%; 25.9%] subjects in the placebo group. There was no significant difference between the two different HRV vaccine regimens.
- In a subset of subjects with pre-vaccination blood samples and seronegative prior to Dose 1, the anti-rotavirus IgA seroconversion rate was 58.4% [95% CI: 51.6%; 64.9%] in the HRV pooled group and 22.5% [95% CI: 15.1%; 31.4%] in the placebo group at one month post Dose 3 of HRV vaccine/placebo. Anti-rotavirus GMC was 67.5 U/ml [95% CI: 51.9; 87.8] in the HRV pooled group and 23.4 U/ml [95% CI: 16.8; 32.5] in the placebo group at one month post Dose 3 of HRV vaccine/placebo.

Conclusions:
Efficacy

- Two doses and three doses of GSK Biologicals' HRV vaccine were effective in preventing severe RV GE caused by the circulating wild-type RV during the period from 2 weeks post Dose 3 up to Visit 6 with a vaccine efficacy of 61.2% [95% CI: 44.0%; 73.2%]. The primary objective of this study was met.

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- Two doses and three doses of GSK Biologicals' HRV vaccine were effective during the period from 2 weeks post Dose 3 up to Visit 6 in protecting infants against:
  - Severe RV GE caused by the circulating G1 wild type with a vaccine efficacy of 64.1% [95% CI: 29.9%; 82.0%].
  - Severe RV GE caused by the non-G1 types with a vaccine efficacy of 59.7% [95% CI: 37.1%; 74.4%].
  - Hospitalisation due to RV GE with a vaccine efficacy of 57.5% [95% CI: 7.2%; 80.8%].
  - Any RV GE caused by the circulating G1 wild type with a vaccine efficacy of 53.4% [95% CI: 42.1%; 62.6%].
  - Any RV GE caused by the non-G1 types with a vaccine efficacy of 43.5% [95% CI: 25.1%; 57.3%].
- There was no statistically significant difference between the 2 Dose and 3 Dose regimens.
- During the period starting from Dose 1 up to Visit 6, vaccine efficacy against severe RV GE caused by the circulating wild type RV was 59.2% [95% CI: 43.1%; 70.9%].
- Vaccine efficacy against all cause severe GE reported during the period from 2 weeks post Dose 3 up to Visit 6 was 30.2% [95% CI: 15%; 42.6%].

Safety

- There was no evidence of a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 6 including SAEs leading to drop out.

Immunogenicity

- The anti-rotavirus IgA antibody seropositivity rate at one month post Dose 3 of HRV vaccine was 63.6% [95% CI: 61.6%; 65.6%] in the HRV pooled group. In a subset of subjects with pre-vaccination blood samples and seronegative prior to Dose 1, the anti-rotavirus IgA seroconversion rate was 58.4% [95% CI: 51.6%; 64.9%] in the HRV pooled group at one month post Dose 3 of HRV vaccine.
- There was no significant difference between the two different HRV vaccine regimens.

Reference: Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. *Scand J Infect Dis.* 1990;22:259-67.

Date of report: 16 March 2009

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-to-protocol
BCG	Bacille Calmette-Guérin
$CCID_{50}$	median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
CI	Confidence interval
CIOMS	Council for the International Organization of Medical Sciences
CRF	Case Report Form
DMEM	Dulbecco's Modified Eagle Medium
ELISA	Enzyme Linked ImmunoSorbent Assay
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric mean concentration
GSK	GlaxoSmithKline
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IS	Intussusception
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
PATH	Program for Appropriate Technology in Health
RCC	Reverse Cumulative Distribution Curve
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction

RV	Rotavirus
SAE	Serious adverse event
SOP	Standard Operating Procedures
U	Units
UL	Upper Limit
VE	Vaccine Efficacy
WHO	World Health Organisation
WRC-GCP	Worldwide Regulatory Compliance-GCP

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 therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Blinding: A procedure in which one or more parties to the trial were kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff were aware of the treatment assignment but the subject was not. When the investigator and sponsor staff who were involved in the treatment or clinical evaluation of the subjects and review/analysis of data were also unaware of the treatment assignments, the study was double blind. This level of blinding was maintained throughout the conduct of the trial, and only when the data was cleaned to an acceptable level of quality was appropriate personnel unblinded or when required in case of a serious adverse event.

Completed: Subjects who completed Visit 6.

Diarrhea: Passage of three or more looser than normal stools (loose or watery stools), within a day.

Diary card: Cards given to the parents /guardians by the investigator to record adverse events following vaccination.

Efficacy follow-up period: Subjects in Cohort 1 South Africa were followed until one year of age. Subjects in Cohort 2 South Africa continued efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi were to continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).

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 analysis.
Gastroenteritis:	Diarrhea with or without vomiting.
Independent Data Monitoring Committee (IDMC):	The IDMC was responsible for safety monitoring during the [rotavirus] trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation 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.
Protocol amendment:	Any change in a clinical protocol which affects the safety of subjects, the scope, design, assessments or scientific validity of the clinical investigation, e.g., dose change, duration of treatment, number of subjects, control group(s), the assessments.
Protocol modification:	Strictly, any change to a clinical protocol that is not considered to be a protocol amendment. In essence, changes to clarify (but not alter) existing design features of a clinical investigation or to encourage greater compliance with the intent of the clinical protocol may be issued as modifications rather than amendments. A protocol modification addresses logistical or administrative aspects of the study (e.g. change of monitor(s), telephone number(s).
Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Regurgitation:	Effortless emesis of swallowed contents.
Rotavirus (RV) GE caused by the circulating wild-type rotavirus strain:	An episode of gastroenteritis occurring after administration of dose 1 of study vaccine in which rotavirus other than vaccine strain was identified in a stool sample collected as soon as possible after the symptoms begin, and preferably not later than 7 days after the start of diarrhoea.
RV season in South Africa:	Based on epidemiological observations in South Africa, the RV season will be considered during the period from March 01 to July 31.

RV season in Malawi:	The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year.
Rotavirus gastroenteritis:	An episode of gastroenteritis occurring after Dose 1 of study vaccine or placebo in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode of gastroenteritis. Stool samples collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before onset of the next gastroenteritis episode, if subject had several episodes of gastroenteritis were considered.
Separate episodes of GE:	Two occurrences of GE symptoms with 5 or more diarrhoea-free days between the episodes.
Serious adverse event:	Any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in disability/incapacity, was a congenital anomaly/birth defect in the offspring of a study subject, an important medical event 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 i.e intussusception.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/milliliter (ml) in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) seronegative for rotavirus.
Seronegative:	A subject whose antibody concentration/titre was below the assay cut-off value.
Seropositive:	A subject whose antibody concentration/titre was greater than or equal to the assay cut-off value.
Severe Rotavirus gastroenteritis:	An episode of GE/RV GE scored ≥11 on the 20-point Vesikari scoring system [Ruuska, 1990].
Subject(s):	Term used throughout the protocol to denote an individual whose parents/guardians have been contacted in order to participate in the clinical study, either as a recipient of the investigational product(s) or as a control.

Treatment: Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.

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, all amendments and administrative changes, the informed consent, and other information that required pre-approval were reviewed and approved by a National IEC in Malawi, an investigational centre IEC or IRB in South Africa, [redacted] and by [redacted]

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 the parent/guardian of each subject prior to the performance of any study-specific procedures. Case report forms (CRFs) 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 multiple sites in South Africa and Malawi. There were 10 principle investigators. Dr. [redacted] was the national coordinating investigator in South Africa and Dr. [redacted] was the principle investigator in Malawi. Dr. [redacted] and Dr. [redacted] reviewed and approved this study report on behalf of all the investigators.

Program for Appropriate Technology in Health (PATH) – Rotavirus initiative and GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium were the study sponsors and GSK Biologicals was responsible for administrative aspects of the study including clinical trial supply management, data management, analysis and reporting.

An Independent Data Monitoring Committee (IDMC), consisting of clinical experts and a biostatistician, monitored the safety aspects of the human rotavirus (HRV) vaccine clinical development. In this capacity, the IDMC periodically reviewed all Serious Adverse Events (SAEs) which were reported during the study till 31 December 2007.

3. INTRODUCTION

Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) among children worldwide. A recent review of epidemiological data estimated that RV infections causes approximately 527 000 (475 000 – 580 000) deaths per year in children less than 5 years of age [WHO, 2007]. Recent reports suggest that RV infection results in approximately 145 000 deaths per year occurring in Sub-Saharan Africa [Steele, 2008]. In South Africa and all sub-Saharan countries, RV is a large health burden in young children accounting for approximately 25% of all hospitalisations due to diarrhoeal diseases in young children less than 5 years of age [Cunliffe, 1998; Steele, 1988; Steele, 2003].

Since the rate of RV illness among young children in the industrialised and less developed countries is high and also because public health interventions to provide safe water, safe food and improved sanitation have only limited impact on the incidence of disease, vaccines are regarded as the first strategy for prevention [Bernstein, 1998].

GSK Biologicals has developed an oral, live, attenuated HRV vaccine for immunisation of infants as a two-dose series in the first year of life. The HRV vaccine was developed from the parent G1P[8] 89-12 vaccine strain with proven efficacy [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002]. The HRV vaccine has been extensively studied in phase I, phase II and phase III clinical studies, and is currently licensed in over 100 countries worldwide.

Two doses of the HRV vaccine tested at different concentrations in phase II clinical trials were immunogenic, well-tolerated with high efficacy demonstrated against RV GE [Vesikari, 2004a; Vesikari, 2004b; Salinas, 2005; Dennehy, 2005; Phua, 2006]. A large phase III study in 63,225 infants demonstrated that the HRV vaccine was not associated with an increased risk of intussusception (IS) during 31 days after vaccination when compared to the placebo [Ruiz Palacios, 2006]. The lack of interference due to co-administration of routine infant vaccinations including oral poliovirus (OPV) vaccine with the HRV vaccine as compared to the placebo group has been established [Phua, 2006; Zaman, 2009].

The main objective of the study was to evaluate the efficacy of HRV vaccine against severe RV GE until one year of age. This study also assessed safety and immunogenicity of the HRV vaccine compared to the placebo. This study report contains the efficacy, safety and immunogenicity analyses of all subjects who have completed Visit 6 at one year of age. Results of the analysis for efficacy and safety data collected at Visit 7 at approximately 18 months of age will be provided in an annex report.

4. STUDY OBJECTIVES

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

Note: The two pooled HRV treatment groups (i.e. HRV 3-Dose group and HRV 2-Dose group) have been referred to as “HRV pooled group”, henceforth in the report.

4.1. Primary objective

- To determine if the GSK Biologicals' HRV vaccine (HRV pooled group) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of the HRV vaccine or the placebo up to Visit 6.

Refer to Section 5.11.1 for the primary endpoint and Section 5.11.7 for the statistical analysis.

4.2. Secondary objectives

Efficacy

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the of HRV vaccine or placebo until Visit 6.

- In South Africa, to assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

Safety

- In all subjects, to assess the safety of two or three doses of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations compared with placebo in terms of AEs leading to drop-out and SAEs during the entire course of the study.

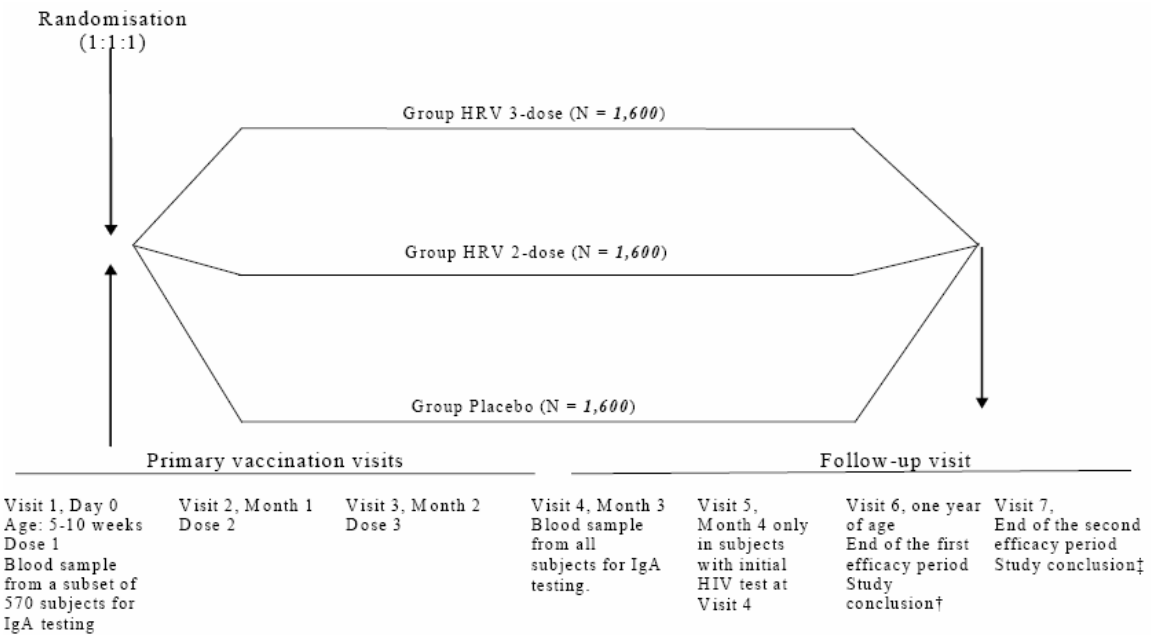
Immunogenicity

- In a subset of subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seropositivity rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after completion of the HRV vaccine course.

Refer to Section 5.11.2 for the secondary endpoints.

5. INVESTIGATIONAL PLAN

5.1. Study design



Testing for HIV was to be ideally performed at Visit 1. If not performed at Visit 1, testing for HIV was offered at Visit 4. Blood sample was to be collected from all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample at the subsequent visit from subjects who tested HIV positive and were asymptomatic for a confirmatory HIV test.
† For subjects in Cohort 1 South Africa
‡ For subjects in Cohort 2 South Africa and the Cohort in Malawi

5.1.1. Overall study design – Description

NOTE: The study design presents details of the study visits only up to Visit 6 which has been considered for the analysis and discussed in this report.

- Experimental design: Double-blind, randomised, placebo-controlled, multi-centre, study with three parallel groups.
- Treatment Groups:
  - **HRV 3-Dose group (also referred to as HRV_3D group)**: Subjects were to receive three doses of HRV vaccine concomitantly with the routine EPI vaccines at 6, 10 and 14 weeks of age.
  - **HRV 2-Dose group (also referred to as HRV_2D group)**: Subjects were to receive two doses of HRV vaccine concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose was to be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding).
  - **Placebo group**: Subjects were to receive three doses of the placebo concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age.

- The study included two cohorts in South Africa (i.e. Cohort 1 South Africa and Cohort 2 South Africa) and one cohort in Malawi. The subjects enrolled in the study as of January 2006 (1,828 subjects) were included in a cohort defined as Cohort 1 South Africa. Enrolment in South Africa was then suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa resumed after the RV season to enroll the total planned number of subjects. The subjects who were enrolled after the RV season were included in a cohort defined as Cohort 2 South Africa. All subjects enrolled in Malawi were included in a cohort defined as Cohort Malawi.
- Study visits: All subjects were to have five study visits (Visit 1, 2, 3, 4 and 6). Subjects who underwent initial Human Immunodeficiency Virus (HIV) testing at Visit 4 were to have one additional visit (Visit 5 at 21-48 days after Visit 4) so that results of the initial HIV test could be communicated to the subject's parents/guardians. If required, a confirmatory HIV test was to be performed at Visit 5 and the parents/guardians were informed about the confirmatory HIV test result in 2 weeks and offered further counselling. For subjects in Cohort 2 South Africa, efficacy and safety follow-up was until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). For all subjects in Malawi, efficacy and safety follow-up was continued until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). These subjects had an additional visit i.e. Visit 7.
- Treatment allocation: Randomised (1:1:1).
- Blinding: Double-blind.
- Control: Placebo group: Three doses of the placebo were to be given concomitantly with the routine EPI vaccines.
- Vaccination schedule: Two-dose or three-dose immunisation in healthy infants at approximately 10 and 14 weeks of age or 6, 10 and 14 weeks of age, respectively.
- Hepatitis B, Bacille Calmette-Guérin (BCG) and Oral Poliovirus (OPV) vaccinations at birth were allowed according to the EPI schedule and their administration was to be documented in the CRF.
- Routine EPI schedule vaccinations (Diphtheria-tetanus-whole-cell pertussis vaccine-Hepatitis B /Haemophilus influenzae type b (DTPw-HB/Hib) and OPV) were to be administered concomitantly with the study vaccine at Visits 1, 2 and 3 following the EPI recommendation (at approximately 6, 10 and 14 weeks of age) and documented in the CRF.
- BCG at Visit 1 was allowed and was to be documented in the CRF. All vaccines administered in the period beginning at birth and ending at study end were to be documented in the CRF.
- No restrictions on feeding of infants before or after the administration of the study vaccine. Height and weight at Visit 1, Visit 4 and Visit 6 were to be recorded.
- Active follow-up for occurrence of GE (diarrhoea) episodes via weekly visit to a subject by study personnel from the day of Dose 1 until Visit 6 for all subjects was performed.

- During each GE episode, a stool sample was to be collected as soon as possible after the symptoms began, and preferably not later than 7 days after the start of diarrhoea. Two occurrences of GE were to be classified as separate episodes if there were 5 or more diarrhoea-free days between the episodes.
- Adverse events (AEs) leading to drop out during the entire study period were recorded. SAEs reported during the entire study period were recorded.
- HIV Testing: During the entire study period, if a subject developed symptoms indicative of AIDS (WHO clinical stages III or IV), or had to be hospitalised with any SAE and HIV testing was not yet performed, HIV testing was to be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. Testing for HIV was to be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV was to be offered at Visit 4. HIV testing performed at hospital admission was recorded in the CRF.

  Results of HIV testing on blood samples collected after informed consent for HIV testing was obtained were to be communicated to the parents/guardians at the subsequent visit/contact. Pre-test and post-test counselling were to be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who tested HIV positive at the initial test and were asymptomatic, a confirmatory HIV test by Polymerase Chain Reaction (PCR) was to be performed at the subsequent visit. If an initial HIV test was done at Visit 4, there was an additional study visit (Visit 5: 21-48 days after Visit 4) so that the parents/guardians could be informed by the study staff of HIV test results and be offered post-test counselling. If required, a confirmatory HIV test was to be performed at Visit 5 and a contact was to be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and be offered further counselling, if necessary.
- Blood samples were to be collected from a subset of subjects (N = 570 subjects; not from subjects in Cohort 2 South Africa) at Visit 1 and from all subjects at Visit 4 to measure anti-rotavirus IgA antibodies.
- Blood samples were to be collected from all subjects whose parent/guardian gave prior consent for HIV testing. An additional blood sample was to be collected for a confirmatory HIV test at the subsequent visit from subjects who tested HIV positive at the initial test and were asymptomatic.
- Data collection: Hard copy CRF.
- Duration of the study: All subjects were to be followed until one year of age, and the intended duration of the study, per subject, was not to exceed a maximum of 10 to 11 months. The study subjects in Cohort 2 South Africa and in the Cohort in Malawi were to be followed during the second year of life i.e. until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008) for Cohort 2 South Africa, and until at least 18 months of age and not more than two years of age in the Cohort in Malawi (last subject last visit not later than 30 January 2009). The study duration will not exceed a maximum of 24 months.

5.2. Study procedures

5.2.1. Outline of study procedures

Table 1 List of study procedures for Cohort 1 and 2 enrolled in South Africa and all subjects enrolled in Malawi

Age	5-10 weeks						
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6	VISIT 7
Timing	Day 0	Month 1	Month 2	Month 3	Month 4	1 year of age	End of 2nd efficacy follow-up period
Sampling timepoint	Pre			Post vacc 3			
Informed consent	•						
Informed consent addendum for HIV testing§	•			•			
Supplementary ICF for using results of HIV testing performed after breast feeding cessation						•	
Supplementary ICF for participation in 2nd efficacy follow-up						•	
Medical history	•						
Medical history for HIV	•						
Check of inclusion criteria	•						
Check of exclusion criteria	•						
Check of elimination criteria		•	•	•		•	•
Check of contraindications	•	•	•				
Randomisation	•						
Physical examination	•	#	#	#		#	#
Pre-vaccination body temperature	•	•	•				
Measure/record height and weight	•			•		•	•
Blood sampling							
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects			
For HIV testing, if and when accepted‡	• (3 ml in South Africa and 1 ml in Malawi)			• (3 ml in South Africa and 1 ml in Malawi)			
Confirmatory HIV testing, if required		• (2 ml in South Africa and 1 ml in Malawi)			• (2 ml in South Africa and 1 ml in Malawi)		
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•	•

Age	5-10 weeks						
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6	VISIT 7
Timing	Day 0	Month 1	Month 2	Month 3	Month 4	1 year of age	End of 2nd efficacy follow-up period
Sampling timepoint	Pre			Post vacc 3			
Study vaccination (HRV or placebo)	●	●	●				
Routine EPI vaccination	●	●	●				
Recording of AEs leading to drop-out	●	●	●	●		●	●
Return of completed diary cards by parents/guardians		●	●	●		●	●
Diary card transcription		●	●	●		●	●
Recording concomitant medication/vaccination	●	●	●	●		●**	●**
Reporting of SAEs occurring throughout the study period, by investigator	●	●	●	●		●	●
Record results of HIV testing		●	●		●		
Inform subjects of HIV result		●	●		●		
Record results of HIV testing after breast feeding ceases						●	●
Study Conclusion						●	●

The shaded area refers to the time point that is not considered for this report.
†Visit 5 was to take place 21-48 days after Visit 4 only in subjects who had an initial HIV test at Visit 4.
●was used to indicate a study procedure which required documentation in the individual CRF.
* = The blood sample was to be collected before administering the dose of vaccine/placebo.
‡Testing for HIV was to be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV was to be offered at Visit 4. The blood sample for the confirmatory test if required was to be obtained at the following visit.
§During the entire study period (from Visit 1 up to Visit 6 for subjects in Cohort 1 in South Africa, from Visit 1 up to Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi), if a child developed symptoms indicative of AIDS (WHO interim stages III or IV), or had to be hospitalised with any SAE and HIV testing had not yet been performed, HIV testing was to be proposed at the site or, in the case of hospitalisation, at hospital admission if possible.
For subjects in Cohort 2 South Africa, HIV testing between Visit 6 – Visit 7 was proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission was recorded in the CRF.
was used to indicate a study procedure which did not require documentation in the individual CRF.
●** Only concomitant medication administered for treatment of GE, AE leading to drop-outs and SAEs was to be recorded during the period.
Visit 7 is for subjects in Cohort 2 South Africa and the Cohort in Malawi only.

5.2.2. Intervals between study visits

The intervals between study visits are presented in Table 2.

Table 2 Intervals between study visits for Cohort 1 and Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

Interval	Size of interval	Adapted interval used for inclusion in ATP cohort for Immunogenicity
1 (Visit 1→Visit 2)	28 to 48 days	21 to 48 days
2 (Visit 2→Visit 3)	28 to 48 days	21 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days	21 to 48 days
4 (Visit 4→Visit 5)	21 to 48 days	-
Visit 6	343-391 days of age	-
Visit 7	1 August 2008 - 15 September 2008 (end of RV season) for Cohort 2 South Africa and until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) for the Cohort in Malawi	

The shaded area refers to the time point that is not considered for this report.

5.3. Selection of study population

Target enrollment was 4,800 subjects (1,600 subjects in each group). Refer to Section 5.11.2 for a detailed description of the criteria used in the estimation of sample size.

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 child between, and including, 5 and 10 weeks of age at the time of the first study vaccination.
- Written informed consent obtained from the parent or guardian of the subject who was of legal age (i.e. parent/guardian ≥ 18 years or older).
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- In South Africa, birth weight > 2000 g or if weight unknown, gestation period > 36 weeks.

5.3.2. Exclusion criteria

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

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or was to be exposed to an investigational or a non-investigational product (pharmaceutical product or device).
- Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids were allowed.)
- History of use of experimental rotavirus vaccine.
- Previous routine vaccination except BCG, HBV and OPV vaccination at birth (was to be documented in the CRF).
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at the time of enrolment. (Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines were to be administered to subjects with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C/Axillary temperature <37.5°C/Rectal temperature <38°C) (Warrants deferral of vaccination).
- Gastroenteritis within 7 days preceding the first study vaccine administration (Warrants deferral of the vaccination).
- Previous confirmed occurrence of RV GE.
- A family history of congenital or hereditary immunodeficiency.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- History of any neurologic disorders or seizures.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

5.3.3. Elimination criteria

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

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

- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids were allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
- Administration of immunoglobulins and/or any blood products during the study period.

5.3.4. Contraindications to subsequent doses of vaccine

GSK Biologicals' HRV vaccine or its placebo

The following AEs constituted absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occurred during the study, the subject could not receive additional doses 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:

- Hypersensitivity reaction due to the vaccine.
- IS.

The following AEs constituted contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs occurred at the time scheduled for vaccination, the subject could be vaccinated at a later date, within the time window specified in the protocol (see Section 5.2.2), or withdrawn at the discretion of the investigator. The subject was to be followed until resolution of the event, as with any AE.

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

5.3.5. Subject completion and withdrawal from study

5.3.5.1. Subject completion

A subject who returned for Visit 6 of the study was considered to have completed the first efficacy period of the study. A subject who could be contacted for Visit 7 (i.e. end of second efficacy period) will be considered to have completed the second efficacy follow-up. The efficacy and safety analyses from Visit 6 to Visit 7 and analyses for the combined efficacy follow-up period (i.e. 2 weeks post Dose 2 up to Visit 7) for subjects in Cohort 2 in South Africa and Cohort Malawi will be presented in an annex report.

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 were to follow 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 was any subject who did not come back for Visit 6.

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 CRF. The investigator documented 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).

5.3.6. Subject withdrawal from 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 have been 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 documented on the Vaccine Administration page of the CRF. The investigator documented 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 vaccine

5.4.1. Description of vaccine

The HRV vaccine and placebo used in this study weredeveloped and manufactured by GlaxoSmithKline Biologicals.

The Quality Control Standards and Requirements for each candidate vaccine were described in separate release protocols and the required approvals were obtained.

Table 3 presents the study vaccines' formulation and lot numbers used in this study.

Table 3 Vaccines, formulation and presentation

Vaccine	Formulation	Presentation	Volume	Lot number
GSK Biologicals' HRV 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 product in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	N/A	[redacted]
GSK Biologicals' Placebo for HRV vaccine	DMEM 2.25 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised product in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	N/A	[redacted]
GSK Biologicals' calcium carbonate buffer	Calcium carbonate 80 mg Xanthane 0.25 % in Water for Injection 1.3 ml	Liquid buffer in pre-filled syringe.	1.3 ml	[redacted]

N/A: Not applicable

5.4.2. Dosage and administration

HRV vaccine or placebo

To prepare GSK Biologicals' HRV vaccine or its placebo for administration, the entire content of the supplied calcium carbonate buffer was injected into the vial of the lyophilised product (vaccine or placebo). The vial was shaken well to resuspend the vaccine. The entire volume of the resuspended product was withdrawn into the same syringe, the transfer device discarded and the resuspended product was then administered promptly as a single oral dose.

The vaccinees were to 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.

If the subject regurgitated or vomited after study vaccine administration, no new study vaccine dose was administered at that visit. The subject could continue to participate in the study and was not excluded from the planned analyses.

The study vaccination regimen is summarised in Table 4.

Table 4 Dosage and Administration

Group	Visit 1	Visit 2	Visit 3
HRV 3-dose	HRV	HRV	HRV
HRV 2-dose	Placebo	HRV	HRV
Placebo	Placebo	Placebo	Placebo

Study vaccines and all routine vaccines administered were documented in the CRF.

5.4.3. Treatment allocation and randomization

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 (1:1:1 ratio) was used to ensure that balance between treatments was maintained: throughout the study, a single treatment number identified uniquely the vaccine doses to be administered to the same subject.

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

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

5.4.3.2. Randomisation of subjects

At Visit 1, subjects were administered the vaccine dose with the lowest treatment number still available at the study site.

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

5.4.3.3. Subset

The subset of 570 subjects (190 subjects per group) from selected sites was to provide a blood sample at Visit 1. No subjects from cohort 2 in South Africa were part of the subset providing blood samples at Visit 1.

5.4.4. Blinding

The study was conducted in a double-blind manner with respect to HRV vaccine, placebo and HRV dosing schedule. The parents/guardians of the subjects, the study personnel and the investigator will be unaware of the administered treatment (HRV vaccine or placebo). Blinding will continue to be maintained for the whole study period (i.e. Visit 6 to Visit 7). This will allow unbiased evaluation of the study vaccine.

A set of individual codes were held at the GSK Biologicals' Central Safety Office. The code was to be broken by the Clinical Safety physician (Study Contact for Emergency Code Break in Sponsor Information page) only in the case of medical events that the investigator/physician in charge of the subject felt that the subject could not be treated without knowing the identity of the study vaccine(s).

The IDMC was informed of each SAE on an ongoing basis. The IDMC had access to the individual codes and could at its discretion decode the SAEs to identify the product administered to any subject and evaluate whether enrolment in the study needed to be halted.

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 at Visit 1 and ending at 31 days post last vaccine dose were to be recorded with generic name of the medication (trade names were allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

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

All vaccines administered in the period beginning at birth and ending at study end were to be documented in the CRF with trade name, route of administration and date(s) of administration.

A prophylactic medication was a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic was considered to be prophylactic when it was given in the absence of fever [rectal temperature < 38°C, oral temperature < 37.5°C or axillary temperature < 37.5°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination was to be recorded in the CRF with generic name of the medication (trade names were 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 a SAE and AE leading to drop-out within the follow-up period for adverse events were recorded in the CRF with generic name of the medication (trade names were allowed for combination drugs only), medical indication (including which AE/SAE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medication administered for the treatment of an SAE, at any time, was recorded on the SAE Report Form.

5.6. Assessment of efficacy variables

5.6.1. Follow-up of GE cases

GE (diarrhoea) was defined as passage of three or more looser than normal stools or watery stools within a day. Active surveillance for occurrence of GE was conducted by the study staff during the entire study period. The study staff made weekly visits to the subject and checked for the occurrence of any GE episodes during the study period.

Parents/guardians of subjects were instructed to contact the study staff in case of episodes of GE. The study staff directed the parents/guardians to the nearest hospital/medical facility as necessary.

5.6.2. Data Collection for GE cases

For each GE episode occurring during the study period, a 'GE diary card' was to be completed by the subject's parents/guardians daily until end of the GE episode. Detailed procedures for follow-up of GE episodes were given in a separate booklet which was provided to all investigators.

The following information was recorded on the GE diary card during each GE episode:

- Temperature, number of vomiting episodes and number of looser than normal stools passed by the subject daily during the GE episode.
- Rehydration or other medication given to the subjects during the GE episode.
- Presence of dehydration during the GE episode.
- Hospitalization during the GE episode.

Following the amendment 1 of the protocol, information on behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration were also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

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

5.7. Assessment of intensity of GE episodes

5.7.1. Vesikari scale to assess intensity of GE episodes

The 20-point scale was used to assess the intensity of GE episodes [Ruuska, 1990]. In this system, based on the information in the diary card points were assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, presence of dehydration or hospitalisation for each episode of GE as shown below in Table 5:

Table 5 The 20-point Vesikari scale to assess intensity of GE episodes

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

*The highest temperature recorded during the episode was scored
**Dehydration was assessed clinically based on World Health Organisation criteria.

A score ≥11 was prospectively defined as severe. A score 7 – 10 was prospectively defined as moderate. A score <7 was prospectively defined as mild.

Information on behavioural symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration were also recorded on the GE diary cards. This additional information allows exploratory analysis of alternative scoring systems.

5.7.2. Collection of stool samples during GE

Parents/guardians of all subjects were asked to collect a stool sample from the subject during each episode of GE (defined as diarrhoea with or without vomiting) between Visit 1 and Visit 6. The GE stool sample was to be collected as soon as possible after illness began and preferably not later than 7 days after the start of diarrhoea. A second GE 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.

The time interval for stool sampling was adapted prior to analysis. Stool samples collected from the start of the GE episode to the minimum of the following two time points either 7 days after the end of the GE episode or the day before onset of the next GE episode if subject had several episodes of GE were used to identify an episode of RV GE.

5.7.3. Analysis of stool samples during GE

Stool samples collected during each episode of GE which occurred from Dose 1 up to Visit 6 were processed at a local designated laboratory and shipped frozen to GSK Biologicals, Belgium. The stool samples were tested at GSK Biologicals, Rixensart, Belgium using Enzyme-Linked Immunosorbent Assay (ELISA) (RotaClone assay from Meridian Bioscience, USA) to detect RV antigen. All stool samples that were RV positive were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) followed by Reverse Hybridization assay at Delft Diagnostic Laboratory, the Netherlands to determine the G and the P types. This technique also allows the discrimination between the G1 vaccine virus and the wild-type G1 RV.

5.8. Assessment of safety variables

5.8.1. AEs/SAEs leading to subject withdrawal or dropout

When an AE leading to subject withdrawal or dropout or 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. All AEs/SAEs leading to subject withdrawal or dropout during the study were recorded on the AE/SAE on the subject's CRF or SAE form as applicable, irrespective of severity or whether or not they were considered related to vaccination.

5.8.2. Serious adverse events

A 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 had 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 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.

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

e. 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 might have interfered or prevented everyday life functions but did not constitute a substantial disruption.

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

g. 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 might have jeopardised the subject or might 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.

Family permission for Physical Autopsy was requested in all cases of fatalities, and where this could not be obtained a verbal autopsy was conducted by the investigator's research staff.

The investigator inquired about the occurrence of SAEs at every visit/contact during the study.

When a SAE occurred, it was the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator then recorded all relevant information regarding the SAE on the SAE Report Form. SAEs were to be reported promptly to GSK Biologicals once the investigator determined that the event met the protocol definition of a SAE. The investigator or designate was required to fax the SAE Report Form to GSK Biologicals' Study Contact for SAE Reporting within 24 hours of his/her becoming aware of these events. In rare circumstances and in the absence of facsimile equipment, notification by telephone was acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone did not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours. Additional or follow-up information relating to the initial SAE report was also to be reported to the GSK Biologicals' Study Contact for SAE Reporting within 24 hours of receipt of such information. After the initial SAE report, the investigator was required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition. In the event of a death determined by the investigator to be related to

vaccination, sending of the fax was to be accompanied by telephone call to the Study Contact for Reporting SAEs.

For all deaths during the study period, the Standard Verbal Autopsy Questionnaire [WHO, 1999] was to be completed in addition to the SAE Report whenever possible and transmitted by the investigator (or designee), irrespective of relationship to vaccination and whether a physical autopsy was performed or not. The Standard Verbal Autopsy Questionnaire did not replace the physical autopsy report.

5.8.3. Assessment of SAEs and AEs leading to subject withdrawal or dropout

The investigator made an assessment of intensity for AEs leading to subject withdrawal or dropout and SAEs reported from Visit 1 to Visit 6 for all subjects. The assessment was based on the investigator's clinical judgement.

The intensity of each SAE/AE leading to withdrawal or dropout recorded in the SAE Report Form/CRF, as applicable, was assigned to one of the following categories:

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

The investigator was obligated to assess the relationship between the investigational product and the occurrence of each AE leading to subject withdrawal or drop-out and each SAE.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AE/SAEs to the individual vaccines administered. The investigator therefore assessed whether the AE/SAE could be causally related to vaccination rather than to the individual vaccines.

Causality of all AEs leading to subject withdrawal or dropout and SAEs was assessed by the investigator using the following question:

In your opinion, did the vaccine(s) possibly contribute to the AE/SAE?

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

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

After the initial SAE report, the investigator was required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition. All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving were reviewed at subsequent visits/contacts.

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.

Clinically significant laboratory abnormalities were followed up until they had returned to normal, or a satisfactory explanation was provided.

GSK Biologicals could request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AEs leading to subject withdrawal or dropout or SAE. The investigator was obliged to assist. If a subject died during participation in the study or during a recognised follow-up period, GSK Biologicals was provided with a copy of any available post-mortem findings, including histopathology.

During the study period (from Visit 1 up until Visit 6), if a child developed symptoms indicative of AIDS (WHO interim stages III or IV), or had to be hospitalised with any SAE and HIV testing had not yet been performed, HIV testing was to be proposed at the site or in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission was to be recorded in the CRF.

Outcome of any AE leading to subject withdrawal or dropout or any SAE reported during the entire study was assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Died (or fatal)

5.9. Assessment of immunogenicity variables

5.9.1. Laboratory assays and time points

Blood samples collected from a subset of 570 subjects at Visit 1 and from all subjects at Visit 4 were centrifuged and the separated serum was stored at –20°C until shipped to GSK Biologicals, Belgium for analysis.

Anti-rotavirus IgA antibody concentrations at Visit 1 (in a subset) and Visit 4 (in all subjects) were measured by ELISA. The assay cut-off was 20 U/ml.

HIV testing

Testing for HIV was to be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV was to be offered at Visit 4.

HIV testing was performed in subjects whose parent/guardian gave consent. For subjects who tested HIV positive at the initial test and were asymptomatic, a confirmatory HIV test was to be performed at the subsequent visit.

HIV tests were performed locally at designated laboratories accredited for HIV testing and using approved test kits.

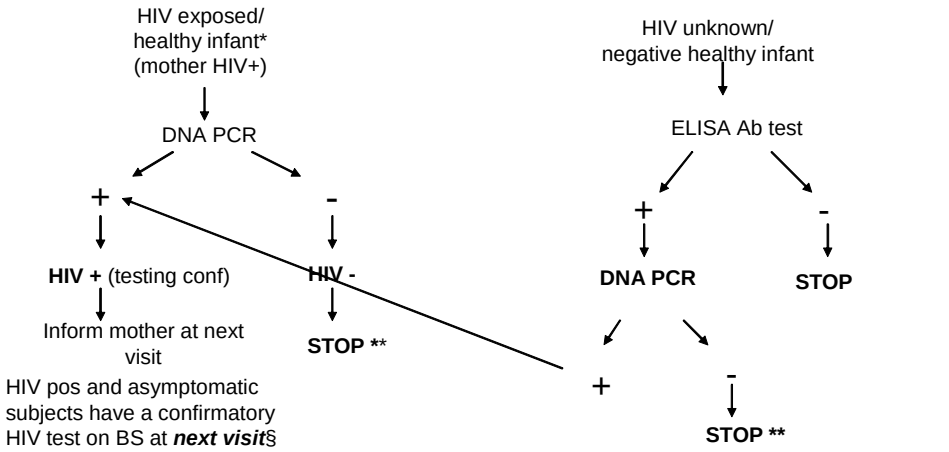
South Africa

HIV testing was to be done according to the algorithm presented in Figure 1 based on the guidelines HIV testing guidelines in children from the Department of Health, South Africa.

National Guidelines in South Africa recommend HIV testing 6 weeks after breast feeding cessation. This testing was done through the usual clinic/paediatric outpatient system. The results of the repeat test after breast feeding ceases were to be recorded in the CRF.

In case of discrepancy between HIV test results at initial and confirmatory tests (HIV positive at initial test, negative at confirmatory test), the HIV test was to be repeated on the confirmatory test blood sample. If the discrepancy remained, the child was to be sent to an ARV roll out centre for HIV repeat test on a new blood sample according to National Guidelines in South Africa.

Figure 1 Algorithm for HIV testing in South Africa



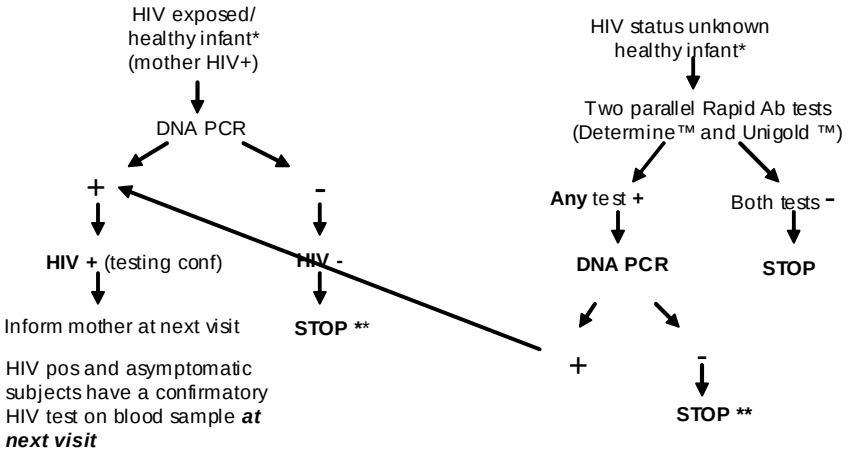
* If infant has signs of HIV infection or has to be hospitalized (WHO interim stages III and IV) and any HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible
** In South Africa: If breast-feeding : repeat test 6 weeks after breast-feeding cessation
§ documented study contact for subjects with confirmatory HIV test

Note: DNA testing using PCR as specified in the Figure 1 is applicable to subjects only up to 18 months of age, whose mothers tested positive for HIV or for whom their mother's status was not known but the ELISA was reactive. ELISA tests would be performed on subjects after 18 months of age. As per the South African Guidelines no DNA PCRs will be performed for subjects after 18 months of age.

Malawi

For all subjects whose parents gave consent for HIV testing, HIV status was to be determined by employing 2 commercially available rapid HIV antibody tests, currently in use by the Malawi's HIV-testing program (Determine and Unigold). If any of the two rapid HIV antibody test results were positive, PCR testing was to be done. Subjects who tested HIV positive at the initial test and were asymptomatic had to undergo PCR testing at the time of the confirmatory test.

Figure 2 Algorithm for HIV testing in Malawi



* If infant has signs of HIV infection (WHO interim stages III or IV) or has to be hospitalised, and any HIV testing has not yet been performed, HIV testing and the concerned Informed Consent will be proposed to the mothers

** If breast-feeding : repeat test at 3 months after breast-feeding cessation.

Table 6 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	Month	Visit no			
GE stool analysis					
At all times from Visit 1 until Visit 6			RV antigen	All	None
Serum analysis					
Timing	Month	Visit no			
Pre	Day 0	1	IgA anti-HRV	Subset of 570 subjects	None
Post-vacc 3	Month 3	4	IgA anti-HRV	All	None
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
HIV test			Serum HIV antibody test (ELISA)	Subjects not exposed to HIV or HIV status unknown	None
			Whole blood DNA PCR	- Subjects not exposed to HIV and positive for HIV antibody - Subjects exposed to HIV	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at the initial HIV test and asymptomatic	None
Malawi					
HIV test			rapid HIV antibody tests	All	None
			Whole blood DNA PCR	Subjects positive by any of the two rapid HIV antibody tests or in case of discrepancy	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at the initial HIV test and asymptomatic	None

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.

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 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).

5.11. Statistical methods

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

5.11.1. Primary endpoint

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains in pooled HRV groups versus the placebo group during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

5.11.2. Secondary endpoints

Efficacy

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 6.
- In South Africa, occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

Safety

- For all subjects, occurrence of AEs/SAEs leading to drop-out throughout the entire study period.
- For all subjects, occurrence of SAEs throughout the entire study period.

Immunogenicity

- In a subset of subjects, seroconversion rate and Geometric Mean concentration (GMC) to anti-rotavirus IgA antibody at Visit 4.

- In all subjects, seropositivity rate and GMC to anti-rotavirus IgA antibody at Visit 4.

5.11.3. Determination of sample size

A total of 4,800 subjects (1,600 subjects in each group) were to be enrolled. Allowing for approximately 15% of subjects who may not be evaluable for analyses of the primary objective, 3,960 evaluable subjects (1,320 subjects in each group) were expected to be evaluable for the analysis of the primary objective.

Considering a 1:1:1 randomisation ratio and various incidence rates expected in the study, Table 7 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy.

Assuming a 2% incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of 3,960 evaluable subjects has 84% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95% CI on vaccine efficacy >0%).

Table 7 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,320 evaluable subjects, N HRV pooled groups = 2,640 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6		
	60%*	70%	80%
1%	50%	69%	86%
1.5%	71%	87%	97%
2%*	84%	95%	99%
3 %	95%	99%	99%

*Anticipated incidence rate

Table 8 presents the power to detect a statistically significant difference between each HRV group and placebo group for a range of vaccine efficacy.

Table 8 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,320 evaluable subjects, N HRV group = 1,320 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6		
	60%	70%	80%
1%	38%	55%	73%
1.5%	57%	76%	90%
2%*	71%	88%	97%
3 %	89%	97%	99%

*Anticipated incidence rate

The study is not powered to compare the efficacy of the 2-dose and the 3-dose schedules.

Estimation of power for the second efficacy period will be indicated in the annex report.

5.11.4. Study cohorts /data sets analyzed

Total vaccinated cohort

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

- a safety analysis based on the total vaccinated cohort included all vaccinated subjects.
- an immunogenicity analysis based on the total vaccinated cohort included all vaccinated subjects for whom immunogenicity data were available.
- an efficacy analysis based on the total vaccinated cohort included all vaccinated subjects.

According-to-protocol (ATP) safety cohort

The ATP safety cohort included all vaccinated subjects:

- who had received at least one dose of HRV vaccine or placebo.
- for whom the randomisation code was not broken.
- who had not received a vaccine forbidden by or not specified in the protocol.
- who had not received a replacement vial, except if the appropriate vaccine was administered in “double-blind replacement”.

ATP efficacy cohort

The ATP efficacy cohort included all subjects from ATP safety cohort:

- who received their full study vaccination course.
- who had entered into the efficacy surveillance period:
  - had follow-up beyond 2 weeks after the last dose of the study vaccination course for analysis of the first and combined efficacy follow-up periods.
- who had no RV other than vaccine strain in diarrhoeal stool samples collected between the day of Dose 1 is administered and 2 weeks after the last dose of the study vaccination course.

ATP immunogenicity cohort

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

- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol,
- with no protocol violation of demographics including 35 to 76 days (5 to 10 weeks) of age at Dose 1,
- who complied with vaccination schedule for HRV vaccine or placebo, i.e. 21-48 days between vaccinations,
- who complied with blood sampling schedule, i.e. 21-48 days between Dose 3 and Visit 4 blood sample,
- for whom immunogenicity data were available, at post sampling timepoint,
- who had no RV other than vaccine strain in GE stool samples collected up to Visit 4,
- who were seronegative for serum anti-rotavirus IgA antibodies or with unknown status of serum anti-rotavirus IgA antibodies on the day of Dose 1 (applicable for the subset of subjects). Refer to Section 5.12.2 for details on the subset.

ATP cohort for seroconversion

The ATP seroconversion cohort included all subjects from the ATP immunogenicity cohort who had pre-vaccination blood sample.

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 primary analysis of safety. The analysis on the ATP safety cohort was to be performed if more than 5% of the vaccinated subjects were excluded from the ATP safety cohort.

The ATP immunogenicity cohort was used for the primary analysis of the seropositivity rate. An analysis of immunogenicity based on the total vaccinated cohort was to be

performed if more than 5% of the vaccinated subjects with post-vaccination immunological results were excluded from the ATP immunogenicity cohort. In such a case, the total vaccinated cohort analyses evaluated whether exclusion from the ATP cohort had biased the results.

The ATP seroconversion cohort was used for the primary analysis of the seroconversion rate.

5.11.5. Derived and transformed data

Demography

Following amendment 1 (24 August 2005), HIV status was determined by ELISA & PCR in subjects having given informed consent at Visit 1 or at Visit 4, if the subject had already completed Visit 1. HIV testing was also possible following adverse events. HIV status was defined positive if, following Visit 1 & Visit 4 procedures, the subject had a positive PCR. HIV status was negative if ELISA testing was negative without positive PCR. There may be bias in analyses in the subset of HIV positive subjects due to a treatment effect on the willingness to HIV testing in some subjects.

Malnutrition was derived from the weight collected at each visit using the Z-score adjusted for sex and age as defined by WHO [WHO Multicentre Growth Reference Study Group, 2006].

Concomitant HIV medication

Concomitant medications were coded using a GSK derived WHO drug dictionary:

- **Therapeutic HIV medications** were any medication belonging to protease inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors.
- **HIV medications** included all therapeutic HIV medications and medication taken for HIV post-exposure prophylaxis.

Efficacy

GE episodes: two occurrences of GE were classified as separate episodes if there were 5 or more diarrhoea-free days between the episodes.

A GE episode was considered to be a RV GE, if a stool sample taken during or not later than 7 days after the episode was ELISA positive for RV. A GE episode without stool sample/result available was not considered in the analysis as a RV GE episode.

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

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting) were calculated by counting the number of days with presence (>0) of looser than normal stool (vomiting). Missing value at a specific day was considered as absence of looser than normal stool (vomiting) on that day.
- The maximum looser than normal stool (vomiting) was defined as the maximum value observed from the number of looser than normal stool (vomiting) recorded daily during the GE episode.
- As the treatment was recorded in the CRF, score associated to the treatment could then be directly derived from the CRF.
- As the dehydration is recorded in the CRF, score associated to the treatment could then be directly derived from the CRF**.**

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

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

Immunogenicity

- The cut-off value of anti-rotavirus IgA antibody defined by the laboratory before the analysis.
- A seronegative subject was a subject whose antibody concentration was below the cut-off value.
- A seropositive subject was a subject whose antibody concentration was greater than or equal to the cut-off value.
- Seroconversion was defined as the appearance of antibodies (i.e. concentration greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- The GMC calculations were performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced.

Safety

For the analysis of SAE/concomitant HIV medication, all vaccinated subjects were considered and subjects who did not report an event were considered as subjects without an event.

5.11.6. Analysis of demographics/baseline characteristics

The mean and standard deviation (SD) of height in cm and weight in kg at Visit 1 and increase in height and weight from Visit 1 to Visits 4 and 6 were calculated per group and overall. The country, racial and gender distributions were presented.

HIV status during the study and malnutrition status at Visits 1, 4 and 6 were summarised by group and overall.

The mean, median, range and SD of age in weeks at each dose of HRV vaccine or placebo were calculated per group and overall. The median, mean, range and SD of age in months at Visit 6 or at last contact if the study visit was not performed were also calculated per group and overall.

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

The percentages of subjects who received concomitant and intercurrent vaccinations were tabulated by group.

All demographic summaries were also performed by country.

5.11.7. Analysis of efficacy

5.11.7.1. Statistical Method

For a specific event, vaccine efficacy for each HRV group and for pooled HRV groups was primarily computed as

VE = vaccine efficacy = (1- RR)*100 = (1 – (ARV/ARU))*100

Where:

ARU =nu/Nu = number of subjects reporting at least one event / total number of subjects in the placebo group.

ARV =dnv/Nv = number of subjects reporting at least one event / total number of subjects in the HRV vaccine group.

RR = relative risk = ARV/ARU

The associated 95% CIs were computed using exact CI for the rate ratio of Poisson distributions [Man-Lai Tang, 2004].

This primary analysis was complemented by:

- two-sided Fisher's exact test.
- Vaccine efficacy was also derived from a Cox regression model on the time to first event with censoring at Visit 6 for subjects without event. The model included the group as fixed effect.
- 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 visit 6 (T). The associated 95% CI's was obtained considering that n followed a Poisson distribution with P*T parameter.
- Number of events prevented by 100 vaccinated infant-years was obtained from 100 times the difference in incidence rate. This associated CI was derived using the method by G. Y. Zou and A. Donner [Zou, 2008].

Note that the exact 95% CI on vaccine efficacy, the 2 sided Fisher exact test, the 95% CI for vaccine efficacy from the Cox model and the 95% CI for the difference in person-year rate may lead to contradiction with respect to statistically significant difference to placebo. When this is happening, this is due to borderline situation (i.e. p-value close to 5%) which leads to statistically significant difference according to the method. In such a case, the exact 95% CI on vaccine efficacy which is the most conservative should be used.

5.11.7.2. Analyses

- The primary endpoint, severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6, was analysed as described in section 5.11.7.1 using the ATP cohort for efficacy. The primary study objective was reached if there was a statistically significant vaccine efficacy. To account for the interim analysis, statistical significant vaccine efficacy at the final analysis had to be based on a 2 sided p-value below 0.038 (O'Brien & Fleming type I error adjusted for the 35 subjects with severe RV GE included in the interim analysis with an interim nominal alpha=0.0155 and the final 136 number of severe RV GE, EAST).
- Secondary endpoints were analysed in a similar way
  - Hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
  - Severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
  - Severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

- Any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the HRV vaccine or placebo until Visit 6.
- In South Africa, severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV Dose 2 or 3) before the beginning of the RV season.
- Severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- RV GE requiring hospitalisation from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

Futher analyses by country were conducted using alternative scoring systems.

Finally, the ATP cohort analyses of efficacy were complemented by total vaccinated cohort analysis for:

- RV GE from Dose 1 until Visit 6,
- RV GE from Dose 1 until 2 weeks post-Dose 3,
- RV GE from Dose 1 until Dose 3.

5.11.8. Analysis of safety

5.11.8.1. Within Group Assessment

The percentage of subjects with SAEs reported during the study period was tabulated by group according to Medical Dictionary for Regulatory Activities (MedDRA) classification, with its exact 95% CI [Clopper, 1934].

The percentage of subjects with SAEs coded to the various MedDRA Preferred Terms (PT) categories for “Pneumonia disease” during the study period were tabulated by group, with its exact 95% CI. “Pneumonia disease” was defined as all PTs under the SOC ‘Infections and Infestations’ that contained the word ‘pneumonia’ and ‘Respiratory, thoracic and mediastinal disorders’.

The percentage of subjects with SAEs associated to MedDRA high level term “Lower respiratory tract and lung infection”, with fatalities and with AEs/SAEs leading to subject drop-out was tabulated by group according to MedDRA classification, with exact 95% CI.

Exploratory safety analyses were performed according to the HIV seropositivity status.

Further summaries were generated by country.

5.11.8.2. Between Group Assessment

The standardised asymptotic 95% CI for the difference between the two groups and the associated 2-sided p-value to detect group difference [Newcombe, 1998: the standardized asymptotic method used within GSK Biologicals is method 6] was computed for the following endpoints assessed over the full vaccination course:

- the percentage of subjects with SAEs reported during the study period according to MedDRA primary preferred terms,
- the percentage of subjects with SAEs causally related to vaccination during the study period according to MedDRA primary PTs,
- the percentage of subjects with SAEs associated to MedDRA high level term "Lower respiratory tract and lung infection", with fatalities and with AEs/SAEs leading to subject drop-out,
- the percentage of subjects with SAEs coded to the various MedDRA PT categories for "Pneumonia disease".

The objective of these analyses was to identify a safety signal as defined by the Council for the International Organization of Medical Sciences (CIOMS) VI working group, i.e. a report or reports of an event with an unknown causal relationship to treatment that was recognized as worthy of further exploration and continuous surveillance. It was recognized that the use of any method to identify safety signals had the potential to identify a large number of events which may or may not have a causal relationship to drug treatment due to multiplicity of endpoints. In order to put any safety signal in perspective, a permutation test was to be conducted to quantify the probability to observe at least one false safety signal according to the threshold p-value defining a signal. In addition, clinical significance and biological plausibility was needed to be accounted before establishing causality.

5.11.9. Analysis of immunogenicity

5.11.9.1. Within Group Assessment

For each treatment group, at each time point that a given antigen was measured,

- Seropositivity/seroconversion rates and their exact 95% CI were tabulated.
- GMCs and their 95% CI were calculated. The 95% CI for the mean of log-transformed concentration was first obtained assuming that log-transformed concentrations were normally distributed with unknown variance. The 95% CI for the GMC was then obtained by exponential-transformation of the 95% CI for the mean of log-transformed concentration.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 4 was displayed using reverse cumulative curves.

Further summaries were generated by country and for the subset of HIV positive subjects.

5.11.9.2. Between Group Assessment

The asymptotic standardised 95% CI for difference in the percentage of subjects who were seropositive for anti-rotavirus IgA antibody concentrations at Visit 4 between groups (each HRV group versus placebo group, pooled HRV groups versus placebo group and HRV_2D group versus HRV_3D group) was computed.

5.11.10. Interim analysis

An interim analysis on efficacy was performed for regulatory purposes.

A planned interim analysis against any RV GE and severe RV GE was performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa for the period starting from 2 weeks after the last dose of the HRV vaccine or placebo up to Visit 6 (or at the last contact if Visit 6 was not performed) or 31 August 2007 (data lock point) whichever was the earliest. The interim analysis was conducted by S-Clinica, Brussels, Belgium, the independent data centre supporting the IDMC in order to maintain the blind. A clinical report of the interim analysis was written. Specific criteria were required to allow dissemination of analyses within and outside GSK. As these were met, the results were combined in a clinical report.

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

5.12.1. Protocol amendments

Amendment 1: The protocol was amended on 24 August 2005 to implement an increase in the sample size and target enrolment numbers. In addition, HIV testing was allowed according to the national guidelines in South Africa. Subjects were to have an additional visit where the results of the HIV test would be communicated. There was a change in the method of data collection from remote data entry to CRF. The amendment also included changes in the protocol to reflect changes in the local clinical practice for care and treatment following feedback from ethics committee.

Amendment 2: The protocol was amended on 27 October 2005 to allow participation of another country, Malawi, in this study. The amendment included certain country-specific changes to reflect Malawi-specific procedures.

Amendment 3: The protocol was amended on 22 February 2006 to implement specific changes for Malawi following ERC review.

Amendment 4: The protocol was amended on 15 May 2006 to implement the IDMC recommendations dated 03 April 2004 to the Malawi-specific amendment.

Amendment 5: The protocol was amended on 10 July 2006 to implement the IDMC recommendation dated 03 April 2004 to the South Africa-specific amendment.

Amendment 6: The protocol was amended on 2 August 2007 to implement the changes for both Cohort 1 and 2 in South Africa as recommended by the Rotavirus Vaccine

Program (RVP) organisation which co-sponsored this study. The changes included specifications on interim analysis to be performed on efficacy data collected from subjects in Cohort 1 and 2 in South Africa, extension of follow-up for efficacy until the end of the second consecutive RV season for Cohort 2 in South Africa and inclusion of some sample size adjustments.

5.12.2. Other changes

- The following efficacy endpoint was not evaluated as the required information was not recorded in the CRF.
  - Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6/7, and from Visit 6 to Visit 7.
- Some of the subjects without pre-vaccination blood samples were erroneously recorded as “no blood sample taken” instead of “not applicable” in the CRF. Hence, these subjects were assumed to be part of the immunogenicity subset for pre-vaccination blood samples and were eliminated from the ATP cohort for immunogenicity for missing pre-vaccination blood samples. However, these subjects were included in the total vaccinated cohort for immunogenicity. Considering that the results of the total vaccinated cohort for immunogenicity are in line with the ATP cohort for immunogenicity, there was no impact on the results of the ATP cohort for immunogenicity.
- Exact p-value for comparing groups with respect to efficacy was based on Fisher exact test instead of the exact p-value associated to the exact CI.
- RV GE episodes due to vaccine type were included in the total vaccinated cohort analyses. As the 4 episodes of RV GE due to vaccine type occurred in the HRV groups, this impacts negatively on the vaccine efficacy.
- To investigate the difference in efficacy by country, additional exploratory analyses were performed, including quantification of the vaccination impact through number of events prevented by 100 vaccinated infant-years and efficacy analysis performed on ATP cohort for efficacy including the subjects who had no RV other than vaccine strain in diarrhoeal stool samples collected between the day of Dose 1 and 2 weeks after the last dose of the study vaccination course.
- Exploratory safety comparisons were included.

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

- Fieldworkers in South Africa and Malawi were to visit the subjects every week to check for the occurrence of diarrhoea during the entire study period. This information was to be transcribed in a “home visit questionnaire”. Some of the fieldworkers were involved in fraudulent activities as they completed the “home visit questionnaire” without meeting the subjects or their parents/guardians. Inspite of these activities, there was no significant impact in the overall data collection as the primary source of data was the diary cards given to the parents/guardians of all

subjects. In addition, the fraudulent visits were small in number compared to the actual home visits performed during the course of the study.

6. STUDY POPULATION RESULTS

6.1. Study dates

The first subject came for the first study visit on 24 October 2005 and the last study visit for the last subject took place on 27 June 2008.

6.2. Subject eligibility and attrition from the study

6.2.1. Number of subjects

Table 9 presents the number of subjects enrolled per country for the total vaccinated cohort.

A total of 4939 subjects were enrolled and received at least one dose of HRV vaccine or placebo.

Supplement 1 presents the number of subjects enrolled by centre and per group for the total vaccinated cohort.

Table 9 Number of subject enrolled in each country (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Country	n	%	n	%	n	%	n	%	n	%
Malawi	590	35.8	592	35.9	1182	35.8	591	36.0	1773	35.9
South Africa	1057	64.2	1059	64.1	2116	64.2	1050	64.0	3166	64.1
South Africa (Cohort 1)	610	37.0	612	37.1	1222	37.1	605	36.9	1827	37.0
South Africa (Cohort 2)	447	27.1	447	27.1	894	27.1	445	27.1	1339	27.1

N = number of subject enrolled in the considered group or in total (sum of all three groups)
n (%) = number (percentage) of subject enrolled in each group or in total for given country.

6.2.2. Study completion and withdrawal from study

Table 10 presents the number of subjects vaccinated, completed and withdrawn from the study with reasons for withdrawal.

Of the 4,939 subjects who received at least one dose of HRV vaccine or placebo, a total of 4,195 subjects (1,420 subjects in the HRV_2D group, 1,383 subjects in the HRV_3D group and 1,392 subjects in the placebo group) completed the study. A total of 744 subjects were withdrawn from the study and the reasons for withdrawal are as follows:

- The parents/guardians of 134 subjects (46 subjects in the HRV_2D group, 44 subjects in the HRV_3D group and 44 subjects in the placebo group) withdrew their child/ward from the study due to SAEs. Randomization code was broken for 6 subjects. Refer to Section 8.2 for details.
- The parents/guardians of 2 subjects (1 subject in the HRV_3D group and 1 subject in the placebo group) withdrew their child/ward from the study due to non-serious AEs.
- A total of 12 subjects (3 subjects in the HRV_2D group, 5 subjects in the HRV_3D group and 4 subjects in the placebo group) were withdrawn from the study due to protocol violations.
- The parents/guardians of 212 subjects (59 subjects in the HRV_2D group, 74 subjects in the HRV_3D group and 79 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 168 subjects (54 subjects in the HRV_2D group, 61 subjects in the HRV_3D group and 53 subjects in the placebo group) migrated from the study area and hence were unable to complete the study.
- A total of 91 subjects (23 subjects in the HRV_2D group, 39 subjects in the HRV_3D group and 29 subjects in the placebo group) with an incomplete vaccination course were lost to follow-up.
- A total of 115 subjects (39 subjects in the HRV_2D group, 42 subjects in the HRV_3D group and 34 subjects in the placebo group) with complete vaccination course were lost to follow-up.
- A total of 10 subjects were withdrawn from the study due to other reasons:
  - Five subjects (2 subjects in the HRV_2D group, 1 subject in the HRV_3D group and 2 subjects in the placebo group) were withdrawn from the study due to non-compliance.
  - One subject in the HRV_2D group was withdrawn from the study because the return dates were not reliable.
  - One subject in the placebo group received vaccination at a regular clinic.
  - The parents/guardians of 2 subjects in the placebo group withdrew consent for their children. [redacted]
  - The consenting parent of one subject in the HRV_3D group passed away. Hence, the subject was withdrawn from the study.

Table 10 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal at visit 6 (Total vaccinated cohort)

	HRV_2D	HRV_3D	HRV_POOL	Placebo	Total
Number of subjects vaccinated	1647	1651	3298	1641	4939
Number of subjects completed	1420	1383	2803	1392	4195
Number of subjects withdrawn	227	268	495	249	744
Reasons for withdrawal :					
Serious Adverse Event	46	44	90	44	134
Non-serious adverse event	0	1	1	1	2
Protocol violation	3	5	8	4	12
Consent withdrawal (not due to an adverse event)	59	74	133	79	212
Migrated/moved from study area	54	61	115	53	168
Lost to follow-up (subjects with incomplete vaccination course)	23	39	62	29	91
Lost to follow-up (subjects with complete vaccination course)	39	42	81	34	115
Others*	3	2	5	5	10

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed visit 6
Withdrawn = number of subjects who did not come for the visit 6
Others* = the reasons for withdrawals are provided in text

6.2.3. Protocol deviations

The number of subjects enrolled and included in the ATP cohort for efficacy along with the reasons for subjects excluded from the ATP cohort for efficacy are summarised in Table 11. Subjects could be attributed more than one elimination code.

Total vaccinated cohort

Of the 4,941 subjects who were enrolled into the study, a total of 4,939 subjects (1,647 subjects in the HRV_2D group, 1,651 subjects in the HRV_3D group and 1,641 subjects in the placebo group) were part of the total vaccinated cohort with at least one dose of HRV vaccine or placebo administered.

ATP cohort for efficacy

Of the 4,939 subjects included in the total vaccinated cohort, 522 subjects were eliminated from the ATP cohort for efficacy for the following reasons:

- The randomisation code was broken for 6 subjects (1 subject in the HRV_2D group, 4 subjects in the HRV_3D group and 1 subject in the placebo group) who experienced an SAE (elimination code 1060).
- A total of 29 subjects (15 subjects in the HRV_2D group, 6 subjects in the HRV_3D group and 8 subjects in the placebo group) were eliminated with code 1070 because the study vaccine dose was not administered according to protocol. Most of the subjects received a replacement vial.
- A total of 404 subjects (115 subjects in the HRV_2D group, 149 subjects in the HRV_3D group and 140 subjects in the placebo group) were eliminated with code

3010 because these subjects did not receive at least one dose of HRV vaccine or placebo.

- A total of 21 subjects (6 subjects in the HRV_2D group, 5 subjects in the HRV_3D group and 10 subjects in the placebo group) were eliminated with code 3020 as these subjects had not entered the efficacy surveillance period.
- GE stool samples from 62 subjects (14 subjects in the HRV_2D group, 9 subjects in the HRV_3D group and 39 subjects in the placebo group) collected between Dose 1 up to 2 weeks post Dose 3 were positive for rotavirus other than the vaccine strain and were assigned code 3030.

Thus, a total of 4,417 subjects (1,496 subjects in the HRV_2D group, 1,478 subjects in the HRV_3D group and 1,443 subjects in the placebo group) were included in the ATP cohort for efficacy.

Table 11 Number of subjects enrolled into the study as well as the number of subjects excluded from ATP cohorts for efficacy with reasons for exclusion

	Total			HRV_2D		HRV_3D		HRV_POOL		Placebo	
Title	n	s	%	n	s	n	s	n	s	n	s
Total enrolled cohort	4941										
Study vaccine dose not administrated but subject number allocated (code 1030)	2	2									
Total vaccinated cohort	4939		100	1647		1651		3298		1641	
Randomisation code broken at the investigator site (code 1060)	6	6		1	1	4	4	5	5	1	1
Study vaccine dose not administered according to protocol (code 1070)	29	31		15	15	6	7	21	22	8	9
At least one study dose not administered (code 3010)	404	428		115	124	149	155	264	279	140	149
Subject not entered the surveillance period of the efficacy follow up period (code 3020)	21	21		6	6	5	5	11	11	10	10
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 3 which may influence efficacy response (code 3030)	62	63		14	14	9	10	23	24	39	39
ATP cohort for efficacy	4417		89.4	1496		1478		2974		1443	

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 12 presents the number of subjects enrolled and excluded from ATP analyses (safety and immunogenicity) along with the reasons for exclusion. Subjects could be attributed more than one elimination code.

ATP cohort for safety

Of the 4,939 subjects included in the total vaccinated cohort, 35 subjects were eliminated from the ATP cohort for safety for the following reasons:

- The randomisation code was broken for 6 subjects (1 subject in the HRV_2D group, 4 subjects in the HRV_3D group and 1 subject in the placebo group) who experienced an SAE (elimination code 1060).
- A total of 29 subjects (15 subjects in the HRV_2D group, 6 subjects in the HRV_3D group and 8 subjects in the placebo group) were eliminated with code 1070 because the study vaccine dose was not administered according to protocol. Most of the subjects received a replacement vial.

Thus, a total of 4,904 subjects (1,631 subjects in the HRV_2D group, 1,641 subjects in the HRV_3D group and 1,632 subjects in the placebo group) were included in the ATP cohort for safety.

ATP cohort for immunogenicity (seropositivity and seroconversion)

Of the 4,904 subjects included in the ATP cohort for safety, a total of 1,481 subjects were eliminated from the ATP cohort for immunogenicity (seropositivity) for the following reasons:

- A total of 22 subjects (6 subjects in the HRV_2D group, 10 subjects in the HRV_3D group and 6 subjects in the placebo group) were eliminated with code 2010 because of protocol violation related to inclusion/exclusion criteria.
- A total of 50 subjects (16 subjects in the HRV_2D group, 15 subjects in the HRV_3D group and 19 subjects in the placebo group) were eliminated with code 2020 as these subjects were initially seropositive.
- A total of 557 subjects (198 subjects in the HRV_2D group, 173 subjects in the HRV_3D group and 186 subjects in the placebo group) who were believed to be in the subset for pre-vaccination blood samples were eliminated with code 2020 as their initial anti-rotavirus antibody status was unknown (Refer to Section 5.12.2).
- A total of 13 subjects (5 subjects in the HRV_2D group, 3 subjects in the HRV_3D group and 5 subjects in the placebo group) were eliminated with code 2040 because they received a medication forbidden in the protocol.
- [redacted]
- A total of 151 subjects (49 subjects in the HRV_2D group, 50 subjects in the HRV_3D group and 52 subjects in the placebo group) were eliminated with code 2080 due to non-compliance with vaccination schedules.
- A total of 72 subjects (24 subjects in each group) were eliminated with code 2090 due to non-compliance with blood sampling schedules.

- A total of 615 subjects (173 subjects in the HRV_2D group, 228 subjects in the HRV_3D group and 214 subjects in the placebo group) were eliminated with code 2100 because serology results were unavailable mainly because blood samples were not collected.

Thus, a total of 3,423 subjects (1,160 subjects in the HRV_2D group, 1,138 subjects in the HRV_3D group and 1,125 subjects in the placebo group) were included in the ATP cohort for immunogenicity (seropositivity).

Of the 3,423 subjects included in the ATP cohort for immunogenicity (seropositivity), a total of 3091 subjects (1054 subjects in the HRV_2D group, 1023 subjects in the HRV_3D group and 1014 subjects in the placebo group) were eliminated from the ATP cohort for immunogenicity (seroconversion) because these subjects were not planned to have pre-vaccination blood samples

Thus, a total of 332 subjects (106 subjects in the HRV_2D group, 115 subjects in the HRV_3D group and 111 subjects in the placebo group) were included in the ATP cohort for seroconversion.

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

	Total			HRV_2D		HRV_3D		Placebo	
Title	n	s	%	n	s	n	s	n	s
Total cohort	4941								
Study vaccine dose not administrated but subject number allocated (code 1030)	2	2							
Total vaccinated cohort	4939		100	1647		1651		1641	
Randomisation code broken at the investigator site (code 1060)	6	6		1	1	4	4	1	1
Study vaccine dose not administered according to protocol (code 1070)	29	31		15	15	6	7	8	9
ATP cohort for safety	4904		99.3	1631		1641		1632	
Protocol violation (inclusion/exclusion criteria) (code 2010)	22	22		6	6	10	10	6	6
Initially seropositive (code 2020)	50	51		16	17	15	15	19	19
Initially unknown antibody status (code 2020)	557	562		198	201	173	175	186	186
Administration of any medication forbidden by the protocol (code 2040)	13	17		5	7	3	3	5	7
Underlying medical condition forbidden by the protocol (code 2050)	1	1		0	0	0	0	1	1
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	151	184		49	60	50	59	52	65
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	72	96		24	35	24	29	24	32
Essential serological data missing (code 2100)	615	750		173	220	228	267	214	263
ATP cohort for immunogenicity	3423		69.3	1160		1138		1125	
Additional Initially unknown antibody status	3091	3091		1054	1054	1023	1023	1014	1014
ATP cohort for seroconversion	332		6.7	106		115		111	

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

Supplement 2 to Supplement 4 present the number of subjects enrolled and excluded from ATP analyses (safety, immunogenicity, and seroconversion) along with the reasons for exclusion, by cohorts in South Africa and by country.

The number of subjects per group and per country with deviations from specifications for age mentioned in the study inclusion criteria and intervals between study visits are presented in Supplement 5 and Supplement 6.

6.3. Demographic characteristics

6.3.1. ATP cohort for efficacy

Demographic characteristics of the ATP cohort for efficacy are summarised in Table 13.

The mean age was 6.3 weeks (range: 2 to 11 weeks) at Dose 1 of HRV vaccine/placebo, 11.3 weeks (range: 8 to 21 weeks) at Dose 2 of HRV vaccine/placebo and 16.2 weeks (range: 12 to 26 weeks) at Dose 3 of HRV vaccine/placebo. The mean age at Visit 6 or last contact if Visit 6 was not performed was 11.6 months (range: 3 to 28 months). Majority of the subjects (96.9%) were of African heritage or African American. 49.4% of the subjects were female and 50.6% of subjects were male.

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

		HRV_2D N = 1496		HRV_3D N = 1478		HRV_POOL N = 2974		Placebo N = 1443		Total N = 4417	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.3	-	6.4	-	6.3	-	6.3	-	6.3	-
	SD	0.90	-	0.98	-	0.94	-	0.96	-	0.95	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	3	-	4	-	3	-	2	-	2	-
	Maximum	11	-	11	-	11	-	11	-	11	-
Age at dose 2 (weeks)	Mean	11.2	-	11.3	-	11.3	-	11.3	-	11.3	-
	SD	1.19	-	1.27	-	1.23	-	1.25	-	1.24	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	8	-	8	-	8	-	9	-	8	-
	Maximum	20	-	21	-	21	-	19	-	21	-
Age at dose 3 (weeks)	Mean	16.2	-	16.3	-	16.2	-	16.3	-	16.2	-
	SD	1.42	-	1.48	-	1.45	-	1.50	-	1.47	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	12	-	13	-	12	-	12	-	12	-
	Maximum	25	-	26	-	26	-	25	-	26	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	11.6	-	11.5	-	11.6	-	11.5	-	11.6	-
	SD	1.24	-	1.40	-	1.33	-	1.39	-	1.35	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	3	-	4	-	3	-	4	-	3	-
	Maximum	19	-	28	-	28	-	19	-	28	-
	Unknown	0	-	1	-	1	-	0	-	1	-
Gender	Female	730	48.8	749	50.7	1479	49.7	702	48.6	2181	49.4
	Male	766	51.2	729	49.3	1495	50.3	741	51.4	2236	50.6
Race	African heritage / African American	1453	97.1	1430	96.8	2883	96.9	1396	96.7	4279	96.9
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other pacific islande	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic/North African heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	2	0.1	3	0.2	5	0.2	1	0.1	6	0.1
	Other	41	2.7	45	3.0	86	2.9	46	3.2	132	3.0
Height at visit 1(cm)	Mean	54.4	-	54.4	-	54.4	-	54.4	-	54.4	-
	SD	2.97	-	3.01	-	2.99	-	3.15	-	3.04	-
	Median	54.0	-	55.0	-	55.0	-	55.0	-	55.0	-
	Unknown	0	-	0	-	0	-	1	-	1	-
Weight at visit 1 (kg)	Mean	4.9	-	4.9	-	4.9	-	4.9	-	4.9	-
	SD	0.70	-	0.71	-	0.70	-	0.69	-	0.70	-
	Median	4.9	-	4.9	-	4.9	-	4.9	-	4.9	-
BMI at visit 1 (kg/m²)	Mean	16.6	-	16.5	-	16.6	-	16.6	-	16.6	-
	SD	2.29	-	2.31	-	2.30	-	2.42	-	2.34	-
	Median	16.4	-	16.3	-	16.3	-	16.4	-	16.3	-
	Unknown	0	-	0	-	0	-	1	-	1	-

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

6.3.2. Total vaccinated cohort

Supplement 7 presents the demographic characteristics of the total vaccinated cohort.

The mean age was 6.4 weeks (range: 2 to 11 weeks) at Dose 1 of HRV vaccine/placebo, 11.3 weeks (range: 7 to 21 weeks) at Dose 2 of HRV vaccine/placebo and 16.3 weeks (range: 12 to 26 weeks) at Dose 3 of HRV vaccine/placebo.

Supplement 8 to Supplement 11 present the demographic characteristics of the total vaccinated cohort for each country.

Supplement 12 presents the number of days between the 3 doses of HRV vaccine/placebo in the total vaccinated cohort. The mean interval between Dose 1 and Dose 2 of HRV vaccine/placebo was 34.8 days and the mean interval between Dose 2 and Dose 3 of HRV vaccine/placebo was 35 days.

Supplement 13 to Supplement 15 present the increase in height (cm) and weight (kg) from Visit 1 to Visits 4 and 6 by group and by country in the total vaccinated cohort.

Supplement 16 to Supplement 18 present the summary of the malnutrition status overall and by country.

Table 14 presents the summary of HIV tests and results performed during the study.

- The percentage of subjects whose parents/guardians gave consent for the HIV test to be performed was 31.4%. Of these subjects, 5.1% of the subjects were tested HIV positive by PCR.

Table 14 Summary of HIV tests and results performed during the study (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
		n	%	n	%	n	%	n	%	n	%
Informed consent signed?	Yes	501	30.4	534	32.3	1035	31.4	516	31.4	1551	31.4
	No	1146	69.6	1117	67.7	2263	68.6	1125	68.6	3388	68.6
		HRV_2D N' = 501		HRV_3D N' = 534		HRV_POOL N' = 1035		Placebo N' = 516		Total N' = 1551	
		n'	%	n'	%	n'	%	n'	%	n'	%
HIV test	Positive	24	4.8	32	6.0	56	5.4	23	4.5	79	5.1
	Negative	476	95.0	502	94.0	978	94.5	493	95.5	1471	94.8
	Unknown	1	0.2	0	0.0	1	0.1	0	0.0	1	0.1

N= number of subject in specified cohort
n = number of subject by informed consent status
N'=number of subject signed informed consent.
n' (%) = number (percentage) of subject resulting a given category
Positive= Subject has at least one positive HIV PCR test results.
Negative= Subject has negative result in HIV ELISA or PCR
Unknown= Subject for whom HIV status is unknown.

Supplement 19 to Supplement 23 present the summary of HIV tests and results performed during the study for each country.

6.3.3. ATP cohort for immunogenicity

Supplement 24 presents the demographic characteristics of the ATP cohort for immunogenicity.

The mean age was 6.3 weeks (range: 5 to 10 weeks) at Dose 1 of HRV vaccine/placebo, 11.2 weeks (range: 9 to 15 weeks) at Dose 2 of HRV vaccine/placebo and 16.1 weeks (range: 13 to 21 weeks) at Dose 3 of HRV vaccine/placebo.

6.4. Concomitant and intercurrent vaccinations

Routine vaccinations according to the local EPI vaccination schedule in each country were to be co-administered with each dose of HRV vaccine/placebo.

A summary of vaccinations co-administered by dose for the total vaccinated cohort is presented in Supplement 25.

Supplement 26 to Supplement 29 present a summary of vaccinations co-administered by dose per country for the total vaccinated cohort.

- A high compliance rate was observed for subjects receiving routine childhood vaccinations concomitantly with at all 3 doses of HRV vaccine/placebo.
- A concomitant dose of OPV was administered to 99.7% of the subjects with Dose 1 of HRV vaccine/placebo, 99.3% of the subjects with Dose 2 of HRV vaccine/placebo and 99.3% with Dose 3 of HRV vaccine/placebo.

A summary of vaccinations other than HRV vaccine or placebo administered from birth up to Visit 6, excluding vaccinations given on the day of HRV vaccine or placebo doses, (intercurrent vaccinations) for the total vaccinated cohort is presented in Supplement 30.

- Majority of the subjects had received a dose of BCG (92.6%) and 88.4% of the subjects had received a dose of OPV before the first dose of HRV vaccine/placebo. The percentages of subjects receiving intercurrent vaccinations were similar in the two groups.
- Since the majority of subjects received routine vaccinations co-administered with each dose of HRV vaccine or placebo, only 2.7% of the subjects received intercurrent vaccinations between Dose 1 and Dose 2 of HRV vaccine/placebo and only 1.1% of the subjects received intercurrent vaccinations between Dose 2 and Dose 3 of HRV vaccine/placebo.
- Majority of the subjects (87.7%) received one dose of Measles vaccine between Dose 3 of HRV vaccine/placebo and Visit 6.

Supplement 31 to Supplement 34 present a summary of vaccinations other than HRV vaccine or placebo administered from birth up to Visit 6, excluding vaccinations given on the day of HRV vaccine or placebo doses, per country for the total vaccinated cohort.

7. EFFICACY RESULTS

7.1. Data sets analyzed

Analysis of efficacy was performed on the ATP efficacy cohort (primary analysis) and 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.

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

Table 15 presents a summary of GE episodes with vaccine strain isolated.

From Dose 1 of HRV vaccine/placebo up to Visit 6, rotavirus vaccine strain was detected in stool samples of 4 GE episodes (3 GE episodes in the HRV_2D group and 1 GE episode in the HRV_3D group).

Table 15 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from dose 1 up to visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
			95% CI				95% CI				95% CI				95% CI	
Parameters or Categories	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Vaccine virus	3	0.2	0.0	0.5	1	0.1	0.0	0.3	4	0.1	0.0	0.3	0	0.0	0.0	0.2

N = number of subject included in each group
n (%) = number (percentage) subjects with vaccine virus in at least one stool sample collected in case of GE episode
95%CI=exact 95% Confidence interval LL=lover limit UL=upper limit

7.2. ATP cohort for efficacy

The ATP cohort for efficacy included 4,417 subjects (1,496 subjects in the HRV_2D group, 1,478 subjects in the HRV_3D group and 1,443 subjects in the placebo group).

7.2.1. Characterisation of GE episodes

A GE episode was defined as occurrence of diarrhoea with or without vomiting. A severe GE/ RV GE episode was defined as an episode of GE/RV GE scored ≥11 on the 20-point Vesikari scoring system [Ruuska, 1990]. Diarrhoea was defined as passage of three or more looser than normal stools (loose or watery stools) within a day.

Table 16 presents the percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6.

- Of all the GE episodes tested, rotavirus was detected in 167 GE episodes in the HRV pooled group (93 GE episodes in the HRV_2D group and 74 GE episodes in the HRV_3D group) and 176 GE episodes in the placebo group.
- Of all the severe GE episodes tested, rotavirus was detected in 56 severe GE episodes in the HRV pooled group (30 severe GE episodes in the HRV_2D group and 26 severe GE episodes in the HRV_3D group) and 70 severe GE episodes in the placebo group.

Table 16 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RVGE episodes from 2 weeks after Dose 3 up to Visit 6 (ATP cohort for efficacy)

		HRV_2D N = 1496		HRV_3D N = 1478		HRV_POOL N = 2974		Placebo N = 1443		Total N = 4417	
Characteristics	Number of Episode	n	%	n	%	n	%	n	%	n	%
GE	0	956	63.9	1000	67.7	1956	65.8	885	61.3	2841	64.3
	1	362	24.2	353	23.9	715	24.0	412	28.6	1127	25.5
	2	132	8.8	93	6.3	225	7.6	101	7.0	326	7.4
	3	38	2.5	24	1.6	62	2.1	27	1.9	89	2.0
	4	8	0.5	5	0.3	13	0.4	13	0.9	26	0.6
	5	0	0.0	3	0.2	3	0.1	4	0.3	7	0.2
	6	0	0.0	0	0.0	0	0.0	1	0.1	1	0.0
	Any	540	36.1	478	32.3	1018	34.2	558	38.7	1576	35.7
RV GE	0	1403	93.8	1404	95.0	2807	94.4	1269	87.9	4076	92.3
	1	93	6.2	74	5.0	167	5.6	172	11.9	339	7.7
	2	0	0.0	0	0.0	0	0.0	2	0.1	2	0.0
	Any	93	6.2	74	5.0	167	5.6	174	12.1	341	7.7
Severe GE	0	1362	91.0	1356	91.7	2718	91.4	1265	87.7	3983	90.2
	1	112	7.5	109	7.4	221	7.4	152	10.5	373	8.4
	2	18	1.2	12	0.8	30	1.0	22	1.5	52	1.2
	3	3	0.2	1	0.1	4	0.1	2	0.1	6	0.1
	4	1	0.1	0	0.0	1	0.0	2	0.1	3	0.1
	Any	134	9.0	122	8.3	256	8.6	178	12.3	434	9.8
Severe RV GE	0	1466	98.0	1452	98.2	2918	98.1	1373	95.1	4291	97.1
	1	30	2.0	26	1.8	56	1.9	70	4.9	126	2.9
	Any	30	2.0	26	1.8	56	1.9	70	4.9	126	2.9

N = number of subject included in each group, for considered efficacy follow-up period
n (%) = number (percentage) subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 35 presents the percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by cohorts in South Africa.

Supplement 36 presents the percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by country.

Supplement 37 presents the percentage of HIV positive subjects with report of GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6.

A total of 2191 GE episodes were reported in the study, stool sample results were not available for a total of 292 episodes. Of these, stool samples were not collected for a total of 262 episodes and stool samples were collected but results were not available for 30 episodes (Supplement 38).

Supplement 39 presents the percentage of GE episodes with missing information for the number of looser than normal stools per day reported from 2 weeks post Dose 3 up to study end.

Table 17 presents a summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes reported from 2 weeks post Dose 3 up to study end using the 20-point Vesikari scale.

When the GE episodes were scored using the 20-point Vesikari scale, 33.5% RV GE episodes in the HRV pooled group (32.3% RV GE episodes in the HRV_2D group and 35.1% RV GE episodes in the HRV_3D group) and 39.8% RV GE episodes in the placebo group were rated as severe (Vesikari score ≥11 points).

Table 17 Number of GE episode and RV GE episodes reported from 2 weeks after Dose 3 up to study end by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%	n	%	n	%
GE	Mild (1-6)	349	45.2	291	45.0	640	45.1	269	34.8
	Moderate (7-10)	247	32.0	212	32.8	459	32.4	288	37.3
	Severe (>10)	161	20.9	136	21.1	297	20.9	210	27.2
	Unknown	15	1.9	7	1.1	22	1.6	6	0.8
	Any	757	98.1	639	98.9	1396	98.4	767	99.2
RV GE	Mild (1-6)	27	29.0	20	27.0	47	28.1	32	18.2
	Moderate (7-10)	36	38.7	28	37.8	64	38.3	73	41.5
	Severe (>10)	30	32.3	26	35.1	56	33.5	70	39.8
	Unknown	0	0.0	0	0.0	0	0.0	1	0.6
	Any	93	100	74	100	167	100	175	99.4

n (%) = number (percentage) of specified event reported in each group by severity using the 20-point Vesikari scale among all specified event reported the considered efficacy period
Any= Any specified symptom reported and scored >0 in Vesikari severity scale
Unknown= symptom reported with Vesikari score =0

Supplement 40 presents a summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes reported from 2 weeks post Dose 3 up to study end using the 20-point Vesikari scale for the HIV positive population.

Supplement 41 presents a summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes reported from 2 weeks post Dose 3 up to study end using the 24-point Clark scale.

Supplement 42 and Supplement 43 present the percentage of subjects with RV GE episodes and severe RV GE episodes by G serotype and P genotype, respectively.

Supplement 44 presents the percentage of subjects who were fully vaccinated (at least 2 weeks post Dose 3) before beginning of RV season in South Africa.

Supplement 45 presents the number of RV GE episodes reported from 2 weeks post Dose 3 of HRV vaccine/placebo up to Visit 6, by G and P types. Supplement 46 to Supplement 49 present the number of RV GE episodes reported from 2 weeks post Dose 3 of HRV vaccine/placebo up to Visit 6, by G and P types per country.

Table 18 presents the number of severe RV GE episodes reported from 2 weeks post Dose 3 of HRV vaccine/placebo up to Visit 6, by G and P types.

Among severe RV GE episodes, G1P[8] wild type was the predominant RV type circulating during the study and was isolated in 17 severe (30.36%) RV GE episodes in the HRV pooled group (8 severe RV GE episodes in the HRV_2D group and 9 severe RV GE episodes in the HRV_3D group) and in 19 severe (27.14%) RV GE episodes in the placebo group.

Other most common rotavirus types isolated were G8P[4] (4 isolates in the HRV_2D group, 5 isolates in the HRV_3D group and 12 isolates in the placebo group), G9P[8] wild type (6 isolates in the HRV_2D group, 2 isolates in the HRV_3D group and 9 isolates in the placebo group) and G12P[6] (5 isolates in the HRV_2D group, 6 isolates in the HRV_3D group and 12 isolates in the placebo group).

Table 18 Number of severe RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy)

Serotype	HRV_2D N'=30		HRV_3D N'=26		HRV_POOL N'=56		Placebo N'=70	
	n	%	n	%	n	%	n	%
G1WT+G2+P4+P8WT	0	0.00	0	0.00	0	0.00	1	1.43
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	1	1.43
G1WT+P4	0	0.00	0	0.00	0	0.00	1	1.43
G1WT+P6	0	0.00	0	0.00	0	0.00	1	1.43
G1WT+P8WT	8	26.67	9	34.62	17	30.36	19	27.14
G2+P4	1	3.33	1	3.85	2	3.57	6	8.57
G2+P4+P8WT	0	0.00	1	3.85	1	1.79	0	0.00
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	4.29
G3+P8WT	2	6.67	0	0.00	2	3.57	2	2.86
G8+P4	4	13.33	5	19.23	9	16.07	12	17.14
G8+P6	1	3.33	0	0.00	1	1.79	0	0.00
G8+P8WT	1	3.33	0	0.00	1	1.79	0	0.00
G9+P8WT	6	20.00	2	7.69	8	14.29	9	12.86
GX	0	0.00	1	3.85	1	1.79	0	0.00
GX+P6	5	16.67	6	23.08	11	19.64	12	17.14
GX+P8WT	2	6.67	1	3.85	3	5.36	3	4.29

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after dose 3 of HRV vaccine or placebo up to Visit 6
GX= G12
Samples collected in case of gastroenteritis episodes from the first dose and the last visit

Supplement 50 to Supplement 53 present the number of severe RV GE episodes reported from 2 weeks post Dose 3 of HRV vaccine/placebo up to Visit 6, by G and P types per country.

Supplement 54 presents the characteristics of RV GE episodes based on Vesikari scale reported from 2 weeks after Dose 3 up to Visit 6. Supplement 55 to Supplement 59 present the characteristics of RV GE episodes based on Vesikari score by G types reported from 2 weeks after Dose 3 up to Visit 6. Supplement 60 presents the characteristics of GE episodes based on Vesikari score reported from 2 weeks after Dose 3 up to Visit 6.

Supplement 61 presents the characteristics of RV GE episodes based on Clark scale reported from 2 weeks after Dose 3 up to Visit 6. Supplement 62 to Supplement 67 present the characteristics of RV GE episodes based on Clark scale by G types reported from 2 weeks after Dose 3 up to Visit 6. Supplement 68 presents the characteristics of GE episodes based on Clark scale reported from 2 weeks after Dose 3 up to Visit 6.

Supplement 69 to Supplement 73 present the duration (in years) of efficacy follow-up from 2 weeks after Dose 3 up to Visit 6, overall and per country.

The mean duration of the efficacy period from 2 weeks after Dose 3 up to Visit 6 was 0.63 years in the HRV pooled group and placebo group.

Supplement 74 to Supplement 78 present the seasonal distribution of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group overall and per country.

Supplement 79 to Supplement 83 present the seasonal distribution of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group overall and per country. Supplement 84 to Supplement 86 present the seasonal distribution of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo per country, while accounting for the subject-months at risk.

There was no distinct RV season in Malawi, while distinct seasonal patterns were observed in South Africa with RV GE infections occuring from March to June.

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

Table 19 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6.

- Significantly fewer subjects in the HRV pooled group reported severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV compared to the placebo group (1.9% versus 4.9%, p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV was 61.2% [95% CI: 44.0%; 73.2%]. The primary efficacy objective of the study was reached since the 2 sided p-value was below 0.038 (criteria specified for fulfilling the primary efficacy objective).

Table 19 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	30	2.0	1.4	2.9	58.7	35.7	74.0	<0.001
HRV_3D	1478	26	1.8	1.2	2.6	63.7	42.4	77.8	<0.001
HRV_POOL	2974	56	1.9	1.4	2.4	61.2	44.0	73.2	<0.001
Placebo	1443	70	4.9	3.8	6.1	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test; Note: 2 sided Fisher exact test comparing 2 doses versus 3 doses=0.686

Table 20 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6 by country.

- There was no significant difference between the HRV_2D group and HRV_3D group in terms of the number of subjects reporting severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6.

- In South Africa, significantly fewer subjects in the HRV pooled group reported severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV compared to the placebo group (0.8% versus 3.3%, p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV was 76.9% [95% CI: 56.0%; 88.4%].

- In Malawi, significantly fewer subjects in the HRV pooled group reported severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV compared to the placebo group (4.0% versus 7.9%, p-value 0.003) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV was 49.4% [95% CI: 19.2%; 68.3%].

Table 20 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by country (ATP cohort for efficacy)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	525	21	4.0	2.5	6.0	49.2	11.1	71.7	0.010
	HRV_3D	505	20	4.0	2.4	6.1	49.7	11.3	72.2	0.010
	HRV_POOL	1030	41	4.0	2.9	5.4	49.4	19.2	68.3	0.003
	Placebo	483	38	7.9	5.6	10.6	-	-	-	-
South Africa	HRV_2D	971	9	0.9	0.4	1.8	72.2	40.4	88.3	<0.001
	HRV_3D	973	6	0.6	0.2	1.3	81.5	55.1	93.7	<0.001
	HRV_POOL	1944	15	0.8	0.4	1.3	76.9	56.0	88.4	<0.001
	Placebo	960	32	3.3	2.3	4.7	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 87 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6 by South Africa cohorts.

Supplement 88 presents the efficacy of the HRV vaccine against severe RV GE episodes with a score ≥ a specific value on the Vesikari scale.

Using the Cox proportional-hazard model, vaccine efficacy against severe RV GE caused by the circulating wild type RV was 62.1% [95% CI: 46.2%; 73.4%]. A total of 5 severe RV GE episodes per 100 infant year could be prevented by vaccination (Supplement 89). In South Africa and Malawi, a total of 4.2 and 6.6 severe RV GE episodes per 100 infant year could be prevented by vaccination, respectively (Supplement 90 and Supplement 91).

7.2.2.1. Vaccine efficacy against severe RV GE for a subset of subjects in South Africa

Supplement 95 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11) RV GE from 2 weeks post Dose 3 up to Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post Dose 3) before/after the RV season in South Africa.

- Significantly fewer subjects who were fully vaccinated (at least 2 weeks post Dose 3) before the RV season in the HRV pooled group reported severe (Vesikari score ≥11) RV GE compared to the placebo group (0.8% versus 4.3%; p-value <0.001). Vaccine efficacy for the subjects who were fully vaccinated (at least 2 weeks post Dose 3) against severe RV GE before the RV season was 80.2% [95% CI: 53.1%; 92.5%].
- Significantly fewer subjects who were not fully vaccinated (at least 2 weeks post Dose 3) before the RV season in the HRV pooled group reported severe (Vesikari score ≥11) RV GE compared to the placebo group (0.7% versus 2.4%; p-value 0.011). Vaccine efficacy for the subjects who were not fully vaccinated (at least 2 weeks post Dose 3) against severe RV GE before the RV season was 71.2% [95% CI: 20.8%; 90.4%].

7.2.3. Vaccine efficacy against severe RV GE by RV serotypes

Table 21 presents the efficacy of the HRV vaccine against severe (Vesikari score ≥11) RV GE from 2 weeks post Dose 3 up to Visit 6 by serotype.

- The number of subjects with report of severe RV GE episodes caused by G1 wild type in the HRV pooled group was lesser compared to the placebo group (0.6% versus 1.6%; p-value: 0.002). Vaccine efficacy against severe RV GE caused by G1 wild type was 64.1% [95% CI: 29.9%; 82.0%].
- When considering all isolated non-G1 types (G2, G3, G8, G9 and G12), significantly fewer number of subjects in the HRV pooled group reported severe RV GE compared to the placebo group (1.3% versus 3.3%; p-value: <0.001). Vaccine efficacy against severe RV GE caused by non-G1 types was 59.7% [95% CI: 37.1%; 74.4%].
- Severe RV GE episodes caused by G2 type was reported by 0.1% of subjects in the HRV pooled group and 0.5% of subjects in the placebo group (p-value 0.017). Vaccine efficacy against severe RV GE caused by G2 type was 79.2% [95% CI: 8.9%; 96.5%].
- Severe RV GE episodes caused by G3 type was reported by 0.1% of subjects in the HRV pooled group and 0.4% of subjects in the placebo group (p-value 0.018). Vaccine efficacy against severe RV GE caused by G3 type was 83.8% [95% CI: 9.6%; 98.4%].
- Severe RV GE episodes caused by G8 type was reported by 0.4% of subjects in the HRV pooled group and 1.0% of subjects in the placebo group (p-value 0.010). Vaccine efficacy against severe RV GE caused by G8 type was 64.4% [95% CI: 17.1%; 85.2%].

- Severe RV GE episodes caused by G9 type was reported by 0.3% of subjects in the HRV pooled group and 0.6% in the placebo group (p-value 0.116). Vaccine efficacy against severe RV GE caused by G9 type was 56.9% [95% CI: -25.9%; 85.5%].
- Severe RV GE episodes caused by G12 type was reported by 0.5% of subjects in the HRV pooled group and 1.0% of subjects in the placebo group (p-value 0.051). Vaccine efficacy against severe RV GE caused by G12 type was 51.5% [95% CI: -6.5%; 77.9%].
- Severe RV GE episodes caused by P[4] type was reported by 0.4% of subjects in the HRV pooled group and 1.4% of subjects in the placebo group (p-value <0.001). Vaccine efficacy against severe RV GE was 70.9% [95% CI: 37.5%; 87.0%].
- Severe RV GE episodes caused by P[6] type was reported by 0.4% of subjects in the HRV pooled group and 0.9% of subjects in the placebo group (p-value 0.052). Vaccine efficacy against severe RV GE was 55.2% [95% CI: -6.5%; 81.3%].
- Severe RV GE episodes caused by P[8] type was reported by 1.1% of subjects in the HRV pooled group and 2.6% of subjects in the placebo group (p-value <0.001). Vaccine efficacy against severe RV GE was 59.1% [95% CI: 32.8%; 75.3%].
- There were 8 subjects (0.5%) in the HRV_2D group and 9 subjects (0.6%) in the HRV_3D group with severe RV GE caused by G1 wild type. Vaccine efficacy was 66.4% [95% CI: 22.3%; 87.0%] in the HRV_2D group and 61.8% [95% CI: 14.3%; 84.4%] in the HRV_3D group.
- There were 22 subjects (1.5%) in the HRV_2D group and 17 subjects (1.2%) in the HRV_3D group with severe RV GE caused by non-G1 wild type. Vaccine efficacy was 54.8% [95% CI: 23.6%; 74.1%] in the HRV_2D group and 64.7% [95% CI: 37.3%; 81.0%] in the HRV_3D group.

Supplement 92 to Supplement 94 present the percentage of subjects reporting severe RV GE episodes and risk difference of the vaccine from 2 weeks post Dose 3 up to Visit 6 overall and by country, respectively.

Table 21 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by serotype (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV_2D	1496	8	0.5	0.2	1.1	66.4	22.3	87.0	0.006
	HRV_3D	1478	9	0.6	0.3	1.2	61.8	14.3	84.4	0.012
	HRV_POOL	2974	17	0.6	0.3	0.9	64.1	29.9	82.0	0.002
	Placebo	1443	23	1.6	1.0	2.4	-	-	-	-
G2	HRV_2D	1496	1	0.1	0.0	0.4	86.2	-7.3	99.7	0.036
	HRV_3D	1478	2	0.1	0.0	0.5	72.1	-46.5	97.2	0.105
	HRV_POOL	2974	3	0.1	0.0	0.3	79.2	8.9	96.5	0.017
	Placebo	1443	7	0.5	0.2	1.0	-	-	-	-
G3	HRV_2D	1496	2	0.1	0.0	0.5	67.8	-79.8	96.8	0.172
	HRV_3D	1478	0	0.0	0.0	0.2	100.0	17.1	100.0	0.014
	HRV_POOL	2974	2	0.1	0.0	0.2	83.8	9.6	98.4	0.018
	Placebo	1443	6	0.4	0.2	0.9	-	-	-	-
G8	HRV_2D	1496	6	0.4	0.1	0.9	61.4	-5.2	87.7	0.048
	HRV_3D	1478	5	0.3	0.1	0.8	67.5	5.8	90.7	0.025
	HRV_POOL	2974	11	0.4	0.2	0.7	64.4	17.1	85.2	0.010
	Placebo	1443	15	1.0	0.6	1.7	-	-	-	-
G9	HRV_2D	1496	6	0.4	0.1	0.9	35.7	-102.3	81.2	0.446
	HRV_3D	1478	2	0.1	0.0	0.5	78.3	-4.8	97.7	0.036
	HRV_POOL	2974	8	0.3	0.1	0.5	56.9	-25.9	85.5	0.116
	Placebo	1443	9	0.6	0.3	1.2	-	-	-	-
G12	HRV_2D	1496	7	0.5	0.2	1.0	55.0	-17.3	84.5	0.087
	HRV_3D	1478	8	0.5	0.2	1.1	47.9	-30.8	80.9	0.146
	HRV_POOL	2974	15	0.5	0.3	0.8	51.5	-6.5	77.9	0.051
	Placebo	1443	15	1.0	0.6	1.7	-	-	-	-
P4	HRV_2D	1496	5	0.3	0.1	0.8	75.9	33.8	92.9	0.002
	HRV_3D	1478	7	0.5	0.2	1.0	65.8	15.9	87.8	0.011
	HRV_POOL	2974	12	0.4	0.2	0.7	70.9	37.5	87.0	<0.001
	Placebo	1443	20	1.4	0.8	2.1	-	-	-	-
P6	HRV_2D	1496	6	0.4	0.1	0.9	55.5	-25.5	86.1	0.109
	HRV_3D	1478	6	0.4	0.1	0.9	54.9	-27.1	86.0	0.110
	HRV_POOL	2974	12	0.4	0.2	0.7	55.2	-6.5	81.3	0.052
	Placebo	1443	13	0.9	0.5	1.5	-	-	-	-
P8	HRV_2D	1496	19	1.3	0.8	2.0	51.8	14.2	73.7	0.0075
	HRV_3D	1478	13	0.9	0.5	1.5	66.6	35.9	83.7	<0.001
	HRV_POOL	2974	32	1.1	0.7	1.5	59.1	32.8	75.3	<0.001
	Placebo	1443	38	2.6	1.9	3.6	-	-	-	-
NonG1	HRV_2D	1496	22	1.5	0.9	2.2	54.8	23.6	74.1	0.001
	HRV_3D	1478	17	1.2	0.7	1.8	64.7	37.3	81.0	<0.001
	HRV_POOL	2974	39	1.3	0.9	1.8	59.7	37.1	74.4	<0.001
	Placebo	1443	47	3.3	2.4	4.3	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

7.2.4. Vaccine efficacy against any RV GE

Table 22 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6.

- Significantly fewer subjects in the HRV pooled group reported any RV GE caused by the circulating wild-type RV compared to the placebo group (5.6% versus 12.1%; p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against any RV GE caused by circulating wild type RV was 53.4% [95% CI: 42.1%; 62.6%].

- There were 74 subjects (5.0%) in the HRV_3D group and 93 subjects (6.2%) in the HRV_2D group with report of any RV GE caused by the circulating wild-type RV. Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.5% [95% CI: 45.2%; 68.8%] in the HRV_3D group and 48.4% [95% CI: 33.3%; 60.4%] in the HRV_2D group.

Table 22 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	93	6.2	5.0	7.6	48.4	33.3	60.4	<0.001
HRV_3D	1478	74	5.0	4.0	6.2	58.5	45.2	68.8	<0.001
HRV_POOL	2974	167	5.6	4.8	6.5	53.4	42.1	62.6	<0.001
Placebo	1443	174	12.1	10.4	13.9	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test
Note: 2 sided Fisher exact test comparing 2 doses versus 3 doses=0.176

Supplement 96 and Supplement 97 present the efficacy of the HRV vaccine against any RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6 by country and by South Africa cohort, respectively.

- In South Africa, significantly fewer subjects in the HRV pooled group reported any RV GE caused by the circulating wild type RV compared to the placebo group (4.2% versus 11.8%, p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 64.2% [95% CI: 52.0%; 73.4%].

- In Malawi, the number of subjects with any RV GE caused by the circulating wild type RV GE in the HRV pooled group was lesser compared to the placebo group (8.3% versus 12.6%, p-value 0.009). Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 34.7% [95% CI: 7.7%; 53.5%].

Supplement 98 to Supplement 100 present the percentage of subjects reporting any RV GE episodes and risk difference of the vaccine from 2 weeks post Dose 3 up to Visit 6 overall and by country, respectively.

Supplement 101 presents the efficacy of the HRV vaccine against any RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6 by RV serotype.

- Fewer subjects in the pooled HRV group reported any RV GE caused by G1 circulating wild type RV compared to the placebo group (1.8% versus 5.4%; p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against any RV GE caused by G1 circulating wild type RV was 67.0% [95% CI: 52.7%; 77.2%].
- Fewer subjects in the pooled HRV group reported any RV GE caused by non-G1 types compared to the placebo group (3.8% versus 6.7%; p-value <0.001) from 2 weeks post Dose 3 up to Visit 6. Vaccine efficacy against any RV GE caused by non-G1 types was 43.5% [95% CI: 25.1%; 57.3%].

Using the Cox proportional-hazard model, vaccine efficacy against any RV GE caused by the circulating wild type RV was 55.6% [95% CI: 45.1%; 64.1%]. A total of 12.67 RV GE episodes per 100 infant year could be prevented by vaccination (Supplement 102). In South Africa and Malawi, a total of 13.61 and 7.97 RV GE episodes per 100 infant year could be prevented by vaccination, respectively (Supplement 103 and Supplement 104).

Supplement 105 presents the percentage of subjects reporting RV GE episodes with a score ≥11 on the Vesikari scale excluding/including 62 subjects with GE during vaccination. Supplement 106 presents the percentage of subjects reporting RV GE episodes with a score ≥11 on the Vesikari scale excluding/including 62 subjects with GE during vaccination and who were excluded from ATP analyses with reasons for exclusion.

7.2.5. Vaccine efficacy against hospitalisation due to RV GE

Table 23 presents the efficacy of the HRV vaccine against hospitalisation due to any RV GE from 2 weeks post Dose 3 up to Visit 6.

- Fewer subjects in the HRV pooled group were hospitalised due to RV GE from 2 weeks post Dose 3 up to Visit 6 (0.5% versus 1.1%; p-value 0.019). Vaccine efficacy against hospitalisation due to RV GE was 57.5% [95% CI: 7.2%; 80.8%].

Table 23 Percentage of subjects hospitalised due to RV GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	10	0.7	0.3	1.2	39.7	-41.3	75.5	0.239
HRV_3D	1478	4	0.3	0.1	0.7	75.6	24.3	94.1	0.006
HRV_POOL	2974	14	0.5	0.3	0.8	57.5	7.2	80.8	0.019
Placebo	1443	16	1.1	0.6	1.8	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 107 presents the efficacy of the HRV vaccine against hospitalisation and/or rehydration due to any RV GE from 2 weeks post Dose 3 up to Visit 6.

7.2.6. Vaccine efficacy against all cause GE

Table 24 presents the efficacy of the HRV vaccine against all cause severe GE episodes.

- All cause severe GE was reported by significantly fewer subjects in the HRV pooled group compared to the placebo group (8.6% versus 12.3%; p-value <0.001). Vaccine efficacy against all cause severe GE was 30.2% [95% CI: 15%; 42.6%].

Table 24 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	134	9.0	7.6	10.5	27.4	8.6	42.4	0.003
HRV_3D	1478	122	8.3	6.9	9.8	33.1	15.3	47.3	<0.001
HRV_POOL	2974	256	8.6	7.6	9.7	30.2	15.0	42.6	<0.001
Placebo	1443	178	12.3	10.7	14.1	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test
Note: 2 sided Fisher exact test comparing 2 doses versus 3 doses=0.514

Supplement 108 and Supplement 109 presents the efficacy of the HRV vaccine against all cause severe GE from 2 weeks post Dose 3 up to Visit 6 by South Africa cohorts and by country, respectively.

Supplement 110 to Supplement 112 presents the efficacy of the HRV vaccine against all cause GE from 2 weeks post Dose 3 up to Visit 6 overall, by South Africa cohorts and by country, respectively.

Supplement 113 and Supplement 114 present the efficacy of the HRV vaccine against hospitalisation and/or rehydration due to GE from 2 weeks post Dose 3 up to Visit 6.

7.2.7. Vaccine efficacy against RV GE by serological status for IgA antibody concentration from 2 weeks post Dose 3 up to Visit 6

Supplement 115 and Supplement 116 present the efficacy of the HRV vaccine against any RV GE and severe RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6 according to the serological status for anti-rotavirus IgA antibodies.

Among the seropositive subjects, 4.1% of the subjects in the HRV pooled group and 9.2% of the subjects in the placebo group reported any RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6, resulting in vaccine efficacy of 55.2% [95% CI: 28.0%; 71.4%]. Severe RV GE was reported in 1.4% of the subjects in the HRV pooled group and 4.6% of the subjects in the placebo group. The vaccine efficacy against severe RV GE was 70.1% [95% CI: 37.6%; 85.2%].

Among the seronegative subjects, 8.2% of the subjects in the HRV pooled group and 12.6% of the subjects in the placebo group reported any RV GE caused by the circulating wild type RV from 2 weeks post Dose 3 up to Visit 6, resulting in vaccine efficacy of 34.8% [95% CI: 13.5%; 51.1%]. Severe RV GE was reported in 2.8% of the subjects in the HRV pooled group and 4.7% of the subjects in the placebo group. The vaccine efficacy against severe RV GE was 39.5% [95% CI: 2.1%; 63.2%].

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

Supplement 117 presents the efficacy of the HRV vaccine against severe RV GE from 2 weeks post Dose 3 up to Visit 6 according to the Clark scale. Supplement 118 presents the efficacy of the HRV vaccine against severe RV GE from 2 weeks post Dose 3 up to Visit 6 according to the Clark scale by country. Supplement 119 presents the efficacy of the HRV vaccine against severe RV GE from 2 weeks post Dose 3 up to Visit 6 according to the Clark scale by cohorts in South Africa. Supplement 120 presents the efficacy of the HRV vaccine against severe RV GE from 2 weeks post Dose 3 up to Visit 6 by ELISA. Supplement 121 presents efficacy of the HRV vaccine against RV GE with a score greater or equal to a specific value on the Clarke scale.

7.3. Total vaccinated cohort analysis

The total vaccinated cohort was used to evaluate vaccine efficacy against severe RV GE due to wild-type RV occurring from Dose 1 onwards.

7.3.1. Vaccine efficacy against severe RV GE during the period from Dose 1 up to Visit 6

Supplement 122 to Supplement 165 present results for vaccine efficacy during the period from Dose 1 up to Visit 6.

Efficacy estimates for the period from Dose 1 up to Visit 6 (mean duration: 0.8 years in each group) were consistent with the results of the primary analysis on the ATP cohort for efficacy for the period from 2 weeks post Dose 3 up to Visit 6.

During the period starting from Dose 1 up to Visit 6, significantly fewer subjects reported severe RV GE (Vesikari score ≥11) in the HRV pooled group caused by the circulating wild type RV compared to the placebo group (2.1% versus 5.1%; p-value <0.001). Vaccine efficacy against severe RV GE caused by the circulating wild type RV during the period from Dose 1 up to Visit 6 was 59.2% [95% CI: 43.1%; 70.9%] (Supplement 147).

- In South Africa, significantly fewer subjects in the HRV pooled group reported severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV compared to the placebo group (0.8% versus 3.4%, p-value <0.001) from Dose 1 up to Visit 6. Vaccine efficacy against severe RV GE caused by the circulating wild type RV during the period from Dose 1 up to Visit 6 was 77.9% [95% CI: 59.2%; 88.6%] (Supplement 149).
- In Malawi, significantly fewer subjects in the HRV pooled group reported severe (Vesikari score ≥11) RV GE caused by the circulating wild type RV compared to the placebo group (4.4% versus 8.0%, p-value 0.003) from Dose 1 up to Visit 6. Vaccine efficacy against severe RV GE caused by the circulating wild type RV during the period from Dose 1 up to Visit 6 was 44.7% [95% CI: 16.1%; 63.4%] (Supplement 149).

7.3.2. Vaccine efficacy against severe RV GE during the period from Dose 1 up to 14 days post Dose 3

Supplement 166 to Supplement 191 present results for vaccine efficacy during the period from Dose 1 to 14 days post Dose 3.

During the period starting from Dose 1 up to 14 days post Dose 3 (mean duration: 0.23 years in each group), 12 subjects (0.4%) from the HRV pooled group and 13 subjects (0.8%) from the placebo group reported severe RV GE caused by the circulating wild type RV. Vaccine efficacy against severe RV GE caused by the circulating wild type RV during the period from Dose 1 up to 14 days post Dose 3 was 54.1% [95% CI: -9.2%; 80.8%] (Supplement 189).

- In South Africa, 1 subject (0.0%) from the HRV pooled group and 4 subjects (0.4%) from the placebo group reported severe RV GE caused by the circulating wild type RV. Vaccine efficacy against severe RV GE caused by the circulating wild type RV during the period from Dose 1 up to 14 days post Dose 3 was 87.6% [95% CI: -25.4%; 99.7%] (Supplement 191).
- In Malawi, 11 subjects (0.9%) from the HRV pooled group and 9 subjects (1.5%) from the placebo group reported severe RV GE caused by the circulating wild type RV. Vaccine efficacy against severe RV GE caused by the circulating wild type RV during the period from Dose 1 up to 14 days post Dose 3 was 38.9% [95% CI: -66.8%; 77.0%] (Supplement 191).

7.3.3. Vaccine efficacy against severe RV GE during the period from Dose 1 up to before Dose 3

Supplement 193 to Supplement 216 present results during the period from Dose 1 to before Dose 3.

During the period starting from Dose 1 up to before Dose 3 (mean duration: 0.19 years in each group), 10 subjects (0.3%) from the HRV pooled group and 8 subjects (0.5%) from the placebo group reported severe RV GE caused by circulating wild type RV. Vaccine efficacy against severe RV GE caused by circulating wild type RV during the period from Dose 1 up to before Dose 3 was 37.8% [95% CI: -81.3%; 77.9%] (Supplement 214).

- In South Africa, 1 subject (0.0%) from the HRV pooled group and 2 subjects (0.2%) from the placebo group reported severe RV GE caused by the circulating wild type RV. Vaccine efficacy against severe RV GE caused by circulating wild type RV during the period from Dose 1 up to before Dose 3 was 75.2% [95% CI: -356.6%; 99.6%] (Supplement 216).
- In Malawi, 9 subjects (0.8%) from the HRV pooled group and 6 subjects (1.0%) from the placebo group reported severe RV GE caused by the circulating wild type RV. Vaccine efficacy against severe RV GE caused by circulating wild type RV during the period from Dose 1 up to before Dose 3 was 25.0% [95% CI: -156%; 76.2%] (Supplement 216).

7.4. Efficacy conclusions

- Two doses and three doses of GSK Biologicals' HRV vaccine were effective in preventing severe RV GE caused by the circulating wild-type RV during the period from 2 weeks post Dose 3 up to Visit 6 with a vaccine efficacy of 61.2% [95% CI: 44.0%; 73.2%]. The primary objective of this study was met.
- Two doses and three doses of GSK Biologicals' HRV vaccine were effective during the period from 2 weeks post Dose 3 up to Visit 6 in protecting infants against:
  - Severe RV GE caused by the circulating G1 wild type with a vaccine efficacy of 64.1% [95% CI: 29.9%; 82.0%].
  - Severe RV GE caused by the non-G1 types with a vaccine efficacy of 59.7% [95% CI: 37.1%; 74.4%].
  - Hospitalisation due to RV GE with a vaccine efficacy of 57.5% [95% CI: 7.2%; 80.8%].
  - Any RV GE caused by the circulating G1 wild type with a vaccine efficacy of 53.4% [95% CI: 42.1%; 62.6%].
  - Any RV GE caused by the non-G1 types with a vaccine efficacy of 43.5% [95% CI: 25.1%; 57.3%].
- Although this study was not adequately powered to evaluate the difference between two regimens, there was no statistically significant difference between the 2 Dose and 3 Dose regimens.

- During the period starting from Dose 1 up to Visit 6, vaccine efficacy against severe RV GE caused by the circulating wild type RV was 59.2% [95% CI: 43.1%; 70.9%].
- Vaccine efficacy against all cause severe GE reported during the period from 2 weeks post Dose 3 up to Visit 6 was 30.2% [95% CI: 15%; 42.6%].

8. SAFETY RESULTS

8.1. Data sets analyzed

Analysis of safety was performed on the total vaccinated cohort that included 4,939 subjects (1,647 subjects in the HRV_2D group, 1,651 subjects in the HRV_3D group and 1,641 subjects in the placebo group).

Table 25 presents the exposure to vaccination by group and overall for the total vaccinated cohort.

A total of 4,513 subjects (91.4%) had received 3 doses of HRV vaccine or placebo.

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

	HRV_2D* N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Total number of doses received	n	%	n	%	n	%	n	%	n	%
1	86	5.2	118	7.1	204	6.2	98	6.0	302	6.1
2	38	2.3	37	2.2	75	2.3	49	3.0	124	2.5
3	1523	92.5	1496	90.6	3019	91.5	1494	91.0	4513	91.4
Any	1647	100	1651	100	3298	100	1641	100	4939	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
* = Subjects in the HRV_2D group received one dose of placebo at 6 weeks of age to maintain the double blinding.

8.2. Serious adverse events

The serious adverse event (SAE) Summary Table(s) are in Section 14.1 and the SAE CIOMS are in Section 14.2.

Table 26 presents the percentage of subjects with SAEs classified by MedDRA SOC occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

- At least one SAE occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 was reported in 9.7% in the HRV pooled group (10.3% in the HRV_2D group and 9.0% in the HRV_3D group) and 11.5% in the placebo group.

Supplement 217 presents the listing of SAEs.

One fatal SAE (Gastroenteritis) was reported for a subject whose onset date was not available and hence this subject was included only in the list of SAEs.

Supplement 218 to Supplement 221 present the percentage of subjects with SAEs classified by MedDRA SOC occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 by South Africa cohorts and by country.

Supplement 222 presents of HIV subjects with SAEs classified by MedDRA SOC occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

Supplement 223 presents the percentage of subjects with SAEs coded to various MedDRA PT categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

- The percentage of HIV positive subjects with report of at least one SAE classified under MedDRA SOC occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 was 0.6% in the HRV pooled group (0.5% in the HRV_2D group and 0.8% in the HRV_3D group) and 0.3% in the placebo group.

- The percentage of subjects with report of at least one SAE occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 classified under MedDRA PT "Pneumonia disease" was 4.0% in the HRV pooled group (4.3% in the HRV_2D group and 3.8% in the HRV_3D group) and 4.5% in the placebo group.

Supplement 224 to Supplement 226 present the statistical comparisons between groups for the percentage of subjects with SAEs classified under MedDRA SOC occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

- From Dose 1 up to Visit 6, at least one SAE was reported for 319 subjects (9.7%) in the HRV pooled group and 189 subjects (11.5%) in the placebo group (p-value: 0.044)

Table 26 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	170	10.3	8.9	11.9	149	9.0	7.7	10.5	319	9.7	8.7	10.7	189	11.5	10.0	13.2
Blood and lymphatic system disorders (10005329)	3	0.2	0.0	0.5	5	0.3	0.1	0.7	8	0.2	0.1	0.5	4	0.2	0.1	0.6
Cardiac disorders (10007541)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	1	0.1	0.0	0.3
Eye disorders (10015919)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Gastrointestinal disorders (10017947)	6	0.4	0.1	0.8	3	0.2	0.0	0.5	9	0.3	0.1	0.5	6	0.4	0.1	0.8
General disorders and administration site conditions (10018065)	2	0.1	0.0	0.4	7	0.4	0.2	0.9	9	0.3	0.1	0.5	6	0.4	0.1	0.8
Immune system disorders (10021428)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Infections and infestations (10021881)	160	9.7	8.3	11.2	135	8.2	6.9	9.6	295	8.9	8.0	10.0	171	10.4	9.0	12.0
Injury, poisoning and procedural complications (10022117)	3	0.2	0.0	0.5	1	0.1	0.0	0.3	4	0.1	0.0	0.3	6	0.4	0.1	0.8
Metabolism and nutrition disorders (10027433)	10	0.6	0.3	1.1	7	0.4	0.2	0.9	17	0.5	0.3	0.8	12	0.7	0.4	1.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Nervous system disorders (10029205)	3	0.2	0.0	0.5	8	0.5	0.2	1.0	11	0.3	0.2	0.6	10	0.6	0.3	1.1
Renal and urinary disorders (10038359)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	4	0.2	0.1	0.6	6	0.4	0.1	0.8	10	0.3	0.1	0.6	6	0.4	0.1	0.8
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	2	0.1	0.0	0.4
Surgical and medical procedures (10042613)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Vascular disorders (10047065)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 227 to Supplement 229 present the statistical comparisons between groups for the percentage of subjects with SAEs coded to the MedDRA PT "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

Supplement 230 presents the percentage of subjects with SAEs classified under MedDRA SOC and PT occurring from Dose 1 of HRV vaccine or placebo up to Visit 6. Supplement 231 to Supplement 234 presents the percentage of subjects with SAEs classified under MedDRA SOC and PT occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 by South Africa cohorts and by country.

Supplement 235 to Supplement 237 present the statistical comparisons between groups for the percentage of subjects with SAEs classified under SOC and PT occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

SAEs assessed as related to vaccination

Table 27 presents the percentage of subjects with SAEs assessed as related to vaccination classified under MedDRA SOC and PT occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

- There were 3 subjects in the HRV pooled group with report of at least one SAE assessed as related to vaccination. Brief description of these events is given below.
- [redacted]
- [redacted]
- [redacted]

[redacted]

Supplement 238 to Supplement 242 present the percentage of subjects with SAEs classified under MedDRA SOC assessed as related to vaccination by South Africa cohorts and by country. Supplement 243 presents the percentage of HIV subjects with SAEs classified under MedDRA SOC assessed as related to vaccination.

Supplement 244 to Supplement 246 present the statistical comparisons between groups for the percentage of subjects with SAEs, classified under MedDRA SOC, assessed as related to vaccination.

Supplement 247 to Supplement 250 present the percentage of subjects with SAEs assessed as related to vaccination classified under MedDRA SOC and PT occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 by country.

Supplement 251 to Supplement 253 present the statistical comparisons between groups for the percentage of subjects with SAEs assessed as related to vaccination classified under MedDRA SOC and PT occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

Table 27 Percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		0	0.0	0.0	0.2	3	0.2	0.0	0.5	3	0.1	0.0	0.3	0	0.0	0.0	0.2
Infections and infestations (10021881)	Otitis media acute (10033079)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Sepsis (10040047)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	0	0.0	0.0	0.2

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

8.2.1. Fatal events

Supplement 254 presents the percentage of subjects with fatalities classified under MedDRA SOC and PT from Dose 1 of HRV vaccine or placebo up to Visit 6.

Supplement 255 presents the percentage of subjects with fatalities due to MedDRA high level term "Lower respiratory tract and lung infections" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

Supplement 256 presents the percentage of subjects with fatalities due to "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

- From Dose 1 of HRV vaccine up to Visit 6, 126 fatal SAEs were reported in the study (83 subjects (2.5%) in the HRV pooled group and 43 subjects (2.6%) in the placebo group). Majority of the fatal SAEs were classified under the SOC MedDRA PT "Gastroenteritis" (27 subjects in the pooled HRV group and 17 subjects in the placebo group). [redacted]
- From Dose 1 of HRV vaccine or placebo up to Visit 6, at least one fatal SAE classified by MedDRA high level term "Lower respiratory tract and lung infections" was reported for 34 subjects (1.0%) in the HRV pooled group (1.1% in the HRV_2D group and 1.0% in the HRV_3D group) and 19 subjects (1.2%) in the placebo group.
- From Dose 1 of HRV vaccine or placebo up to Visit 6, fatal SAEs coded to the MedDRA PT "Pneumonia disease" were reported for 42 subjects (1.3%) in the HRV pooled group and 20 subjects (1.2%) in the placebo group.

Supplement 257 to Supplement 259 present the statistical comparisons between groups for the percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6. Supplement 260 to Supplement 262 present the statistical comparisons between groups for the percentage of subjects with fatalities due to "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6. Supplement 263 to Supplement 265 present the statistical comparisons between groups for the percentage of subjects with fatalities due to "Lower respiratory tract and lung infections" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6.

- From Dose 1 of HRV vaccine or placebo up to Visit 6, at least one fatal SAE due to"Pneumonia disease" was reported for 42 subjects (1.3%) in the HRV pooled group and 20 subjects (1.2%) in the placebo group (p-value 0.871) (Supplement 262).
- From Dose 1 of HRV vaccine or placebo up to Visit 6, at least one fatal SAE due to "Lower respiratory tract and lung infections" was reported for 34 subjects (1.0%) in the HRV pooled group and 19 subjects (1.2%) in the placebo group (p-value 0.683) (Supplement 265).

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

Table 28 presents the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA, SOC and PT occurring from Dose 1 up to Visit 6.

Supplement 269 presents the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA SOC from Dose 1 up to Visit 6. Supplement 270 to Supplement 272 present the statistical comparison between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA SOC from Dose 1 up to Visit 6.

Supplement 273 to Supplement 275 present the statistical comparison between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA SOC and PT from Dose 1 up to Visit 6.

- The percentage of subjects with at least one symptom leading to drop out was 2.8% in the HRV pooled group (2.8% in the HRV_2D group and 2.7% in the HRV_3D group) and 2.7% in the placebo group.
- Among the AEs/SAEs leading to withdrawal, Pnuemonia (0.7% versus 0.8%), GE (0.6% versus 0.7%), and Bronchopnuemonia (0.2% verus 0.2%), respectively in the HRV pooled group and the placebo group were the most commonly reported symptoms.
- There was no potential imbalance between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA SOC and PT from Dose 1 up to Visit 6 (p-value being above 0.05).

Table 28 Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		46	2.8	2.1	3.7	45	2.7	2.0	3.6	91	2.8	2.2	3.4	44	2.7	2.0	3.6
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Lymphadenitis (10025188)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Vomiting (10047700)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
General disorders and administration site conditions (10018065)	Death (10011906)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	4	0.1	0.0	0.3	0	0.0	0.0	0.2
	Pyrexia (10037660)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sudden death (10042434)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	2	0.1	0.0	0.4
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Bronchiolitis (10006448)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Bronchopneumonia (10006469)	7	0.4	0.2	0.9	0	0.0	0.0	0.2	7	0.2	0.1	0.4	3	0.2	0.0	0.5
	Gastroenteritis (10017888)	10	0.6	0.3	1.1	9	0.5	0.2	1.0	19	0.6	0.3	0.9	11	0.7	0.3	1.2
	Herpes simplex (10019948)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Malaria (10025487)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	2	0.1	0.0	0.4
	Meningitis (10027199)	2	0.1	0.0	0.4	1	0.1	0.0	0.3	3	0.1	0.0	0.3	0	0.0	0.0	0.2
	Meningitis bacterial (10027202)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Otitis media acute (10033079)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Pneumocystis jiroveci pneumonia (10064108)	3	0.2	0.0	0.5	3	0.2	0.0	0.5	6	0.2	0.1	0.4	2	0.1	0.0	0.4
	Pneumonia (10035664)	10	0.6	0.3	1.1	12	0.7	0.4	1.3	22	0.7	0.4	1.0	13	0.8	0.4	1.4
	Pulmonary tuberculosis (10037440)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Respiratory tract infection (10062352)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sepsis (10040047)	5	0.3	0.1	0.7	4	0.2	0.1	0.6	9	0.3	0.1	0.5	0	0.0	0.0	0.2
Injury, poisoning and procedural complications	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
(10022117)																	
	Vaccination complication (10046861)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Dehydration (10012174)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	3	0.1	0.0	0.3	1	0.1	0.0	0.3
	Kwashiorkor (10023504)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Malnutrition (10061273)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Marasmus (10026820)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Febrile convulsion (10016284)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Hydrocephalus (10020508)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	2	0.1	0.0	0.4
	Status epilepticus (10041962)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Aspiration (10003504)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Dyspnoea (10013968)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Grunting (10018762)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Respiratory arrest (10038669)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Respiratory distress (10038687)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

8.4. Other significant adverse events

Supplement 276 presents the summary of subjects with IS occurring from Dose 1 of HRV vaccine up to Visit 6.

One subject from the HRV_3D group reported IS. A brief decription is presented below.

[redacted] This SAE was assessed by the investigator not to be causally related to vaccination.

8.5. Concomitant medications /vaccinations

Concomitant vaccinations are summarised in Section 6.4. Exploratory analysis was performed on subjects who received HIV medication (for post exposure prophylaxis and for treatment) during this study.

Supplement 277 to Supplement 281 present the summary of concomitant HIV medication during the study per cohort in South Africa and per country, respectively.

- A total of 5 subjects (1 subject in the pooled HRV group and 4 subjects in the placebo group) received therapeutic HIV medication and a total of 207 subjects (131 subjects in the pooled HRV group and 76 subjects in the placebo group) received HIV medication during the course of the study.

8.6. Safety conclusions

- There was no evidence of a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 6 including SAEs leading to drop out.

9. IMMUNOGENICITY RESULTS

9.1. Data sets analysed

Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and 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.

9.2. ATP cohort for immunogenicity (seropositivity and seroconversion)

The ATP cohort for seropositivity analysis consisted of 3,423 subjects (1,160 subjects in the HRV_2D group, 1,138 subjects in the HRV_3D group and 1,125 subjects in the placebo group).

The ATP cohort for seroconversion analysis consisted of 332 subjects (106 subjects in the HRV_2D group, 115 subjects in the HRV_3D group and 111 subjects in the placebo group).

The seroconversion rate was calculated for only a subset of subjects from whom blood samples were drawn at Visit 1 (N = 570 subjects; not from subjects in Cohort 2 South Africa) and seronegative for anti-RV IgA antibodies prior to Dose 1. The seropositivity rate was calculated for all subjects with post-vaccination blood samples.

9.3. Serum anti-rotavirus IgA antibody response

The anti-rotavirus IgA antibody GMC and seropositivity rates at one month post Dose 3 of HRV vaccine/placebo are presented in Table 29.

The anti-rotavirus IgA antibody GMC and seroconversion rates at one month post Dose 3 of HRV vaccine/placebo are presented in Table 30.

Supplement 284 to Supplement 285 present the anti-rotavirus IgA GMC and seropositivity rates at one month post Dose 3 of HRV vaccine/placebo by country.

Supplement 286 to Supplement 289 present the anti-rotavirus IgA GMC and seroconversion rates at one month post Dose 3 of HRV vaccine/placebo by country.

- At one month post Dose 3 of HRV vaccine/placebo, 63.6% [95% CI: 61.6%; 65.6%] subjects were seropositive in the HRV pooled group and 23.3% [95% CI: 20.8%; 25.9%] subjects were seropositive in the placebo group indicating these subjects may have been exposed to RV infection during vaccination.

- In a subset of subjects with pre-vaccination blood samples and seronegative prior to Dose 1, the anti-rotavirus IgA seroconversion rate was 58.4% [95% CI: 51.6%; 64.9%] in the HRV pooled group and 22.5% [95% CI: 15.1%; 31.4%] in the placebo group at one month post Dose 3 of HRV vaccine/placebo. Anti-rotavirus GMC was 67.5 U/ml [95% CI: 51.9; 87.8] in the HRV pooled group and 23.4 U/ml [95% CI: 16.8; 32.5] in the placebo group at one month post Dose 3 of HRV vaccine/placebo.

Table 29 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity - seropositivity)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	106	0	0.0	0.0	3.4	<20	-	-
	PIII(M3)	1160	756	65.2	62.4	67.9	72.5	65.2	80.6
HRV_3D	PRE	115	0	0.0	0.0	3.2	<20	-	-
	PIII(M3)	1138	706	62.0	59.1	64.9	67.9	60.8	75.9
HRV_POOL	PRE	221	0	0.0	0.0	1.7	<20	-	-
	PIII(M3)	2298	1462	63.6	61.6	65.6	70.2	65.0	75.8
Placebo	PRE	111	0	0.0	0.0	3.3	<20	-	-
	PIII(M3)	1125	262	23.3	20.8	25.9	21.8	19.8	24.0

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Table 30 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity - seroconversion)

				≥ 20 U/ML			GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	106	0	0.0	0.0	3.4	<20	-	-
	PIII(M3)	106	57	53.8	43.8	63.5	56.6	38.9	82.3
HRV_3D	PRE	115	0	0.0	0.0	3.2	<20	-	-
	PIII(M3)	115	72	62.6	53.1	71.5	79.4	54.7	115.2
HRV_POOL	PRE	221	0	0.0	0.0	1.7	<20	-	-
	PIII(M3)	221	129	58.4	51.6	64.9	67.5	51.9	87.8
Placebo	PRE	111	0	0.0	0.0	3.3	<20	-	-
	PIII(M3)	111	25	22.5	15.1	31.4	23.4	16.8	32.5

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post time points
n (%) = number (percentage) of subjects who seroconverted
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = blood sample taken one month after Dose 3 of HRV vaccine/placebo (visit 4)
PRE = pre-vaccination

Table 31 presents the anti-rotavirus IgA antibody GMCs calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at Visit 4.

Supplement 290 to Supplement 293 present the anti-rotavirus IgA antibody GMCs calculated on subjects who were seropositive for anti-rotavirus IgA antibodies at Visit 4 by country.

Table 31 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity - seropositivity)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	756	209.0	189.0	231.2
HRV_3D	PIII(M3)	706	219.3	196.4	244.9
HRV_POOL	PIII(M3)	1462	213.9	198.6	230.4
Placebo	PIII(M3)	262	285.5	233.4	349.3

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Table 32 presents the anti-rotavirus IgA antibody GMCs calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at Visit 4.

Supplement 294 to Supplement 297 present the anti-rotavirus IgA antibody GMCs calculated on subjects who seroconverted for anti-rotavirus IgA antibodies at Visit 4 by country.

Table 32 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity - seroconversion)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	57	250.9	168.7	373.0
HRV_3D	PIII(M3)	72	273.6	190.5	392.9
HRV_POOL	PIII(M3)	129	263.3	202.2	342.8
Placebo	PIII(M3)	25	432.8	219.7	852.7

GMC = geometric mean antibody concentration calculated on subjects with concentration ≥ 20 U/ML
N = number of subjects who were seronegative for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Table 33 presents the difference in anti-rotavirus IgA antibody seropositivity rate at Visit 4. Table 34 presents the ratio of anti-rotavirus IgA antibody GMCs at Visit 4.

- A significant difference was detected between the HRV pooled group and (minus) the placebo group for the difference in the anti-rotavirus IgA antibody seroconversion rate at Visit 6 since the two-sided asymptotic standardised 95% CI for the difference between groups did not contain the value 0%.

- A significant difference was not detected between the HRV_3D group and (over) HRV_2D as the two-sided 95% CIs for the ratio of anti-rotavirus IgA antibody GMCs at Visit 4 contained the value 1.

Table 33 Difference between groups in percentage of subjects seropositive for anti-rotavirus IgA antibody at visit 4 (ATP cohort for immunogenicity - seropositivity)

						Difference in seropositivity rate			
								95 % CI	
Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HRV_2D	1160	65.2	HRV_3D	1138	62.0	HRV_3D - HRV_2D	-3.13	-7.06	0.80
Placebo	1125	23.3	HRV_2D	1160	65.2	HRV_2D - Placebo	41.88	38.13	45.50
Placebo	1125	23.3	HRV_3D	1138	62.0	HRV_3D - Placebo	38.75	34.94	42.43
Placebo	1125	23.3	HRV_POOL	2298	63.6	HRV_POOL - Placebo	40.33	37.11	43.42

N = number of subjects with available results
% = percentage of subjects who were seropositive
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Table 34 Ratios of anti-rotavirus IgA antibody GMCs at visit 4 between HRV groups (ATP cohort for immunogenicity - seropsotivity)

						GMC ratio			
								95% CI	
Group description	N	GMC	Group description	N	GMC	Ratio order	Value	LL	UL
HRV_3D	1138	67.909	HRV_2D	1160	72.511	HRV_3D /HRV_2D	0.94	0.80	1.09

GMC = geometric mean antibody concentration
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

9.3.1. Serum anti-rotavirus IgA antibody response in HIV positive subjects

Supplement 298 to Supplement 301 present the immunogenicity results of the HIV positive subjects.

The results observed in HIV positive subjects are similar to those observed in healthy subjects.

9.4. Total vaccinated cohort

Supplement 302 to Supplement 310 present the results of the total vaccinated cohort analyses.

The immunogenicity (seropositivity and seroconversion) results of the total vaccinated cohort analysis were consistent with those obtained in the ATP cohort for immunogenicity.

- In South Africa, the percentage of subjects who were initially seropositive was 8.1% [95% CI: 4.6%; 13.0%] in the pooled HRV group and 12.2% [95% CI: 6.3%; 20.8%] in the placebo group.

- In Malawi, the percentage of subjects who were initially seropositive was 13.5% [95% CI: 8.1%; 20.7%] in the pooled HRV group and 10.4% [95% CI: 4.3%; 20.3%] in the placebo group.
- The anti-rotavirus IgA antibody seropositivity rate at one month post Dose 3 of HRV vaccine was 63.2% [95% CI: 61.4%; 65.0%] in the HRV pooled group and 25.2% [95% CI: 22.9%; 27.6%] in the placebo group.
- The anti-rotavirus IgA antibody seroconversion rate was 58.4% [95% CI: 51.9%; 64.7%] in the HRV pooled group and 22.0% [95% CI: 14.9%; 30.6%] in the placebo group at one month post Dose 3 of HRV vaccine/placebo.

9.5. Immunogenicity conclusions

- The anti-rotavirus IgA antibody seropositivity rate at one month post Dose 3 of HRV vaccine was 63.6% [95% CI: 61.6%; 65.6%] in the HRV pooled group. In a subset of subjects with pre-vaccination blood samples and seronegative prior to Dose 1, the anti-rotavirus IgA seroconversion rate was 58.4% [95% CI: 51.6%; 64.9%] in the HRV pooled group at one month post Dose 3 of HRV vaccine.
- There was no significant difference between the two different HRV vaccine regimens.

10. DISCUSSION AND OVERALL CONCLUSIONS

10.1. Discussion

This phase III, double-blind study was conducted in South Africa and Malawi to evaluate the efficacy of 2 doses and 3 doses of HRV vaccine when given concomitantly with routine EPI vaccines. The safety and immunogenicity of the HRV vaccine/placebo was also evaluated.

Two and three doses of the HRV vaccine were found to be effective against severe RV GE (combined vaccine efficacy: 61.2% [95% CI: 44.0%; 73.2%]; p-value: <0.001) during the period starting from 2 weeks post Dose 3 up to Visit 6 in a challenging setting in Africa with a high prevalence of HIV infection, malnutrition and other infections and limited health care resources.

In this study, while G1P[8] was one of the most prevalent stains identified from GE stool samples collected from the placebo group during the period starting from 2 weeks post Dose 3 up to Visit 6, it represented only 50% of the identified strains. The other prevalent strains were G2P[4], G8P[4], G9P[8] and G12P[6]. G8P[4], G9P[8] and G12P[6] were the most prevalent strains in Malawi while G1P[8] and G2P[4] were predominant in South Africa. Vaccine efficacy observed against circulating wild types G1 type was 64.1% [95% CI: 29.9%; 82.0%] and against non-G1 types was 59.7% [95% CI: 37.1%; 74.4%]. G1P[8] has been the most predominant strain observed in other efficacy trials conducted in Latin America, Europe and Asia [Linhares, 2008; Vesikari, 2007; GlaxoSmithKline Biologicals' Clinical Report Rota-028; 029; 030].

Vaccine efficacy against severe RV GE was 76.9% [95% CI: 56.0%; 88.4%] in South Africa and 49.4% [95% CI: 19.2%; 68.3%] in Malawi. Vaccine efficacy results against severe RV GE observed in South Africa were comparable to the efficacy results obtained in earlier efficacy studies conducted in Latin America [Ruiz Palacios, 2006]. Potential factors that may have contributed to the difference in estimates between the two countries might include seasonality, time of enrolment in relation with the rotavirus season, the level of rotavirus exposure which led to the high seroconversion rate observed in the placebo group in Malawi, differences in severity of RV GE episodes in both countries, the difference in the RV types isolated and potential differences in underlying host characteristics in Malawi compared to South Africa. While there was no distinct RV season in Malawi, a clear seasonal pattern was observed in South Africa with the RV GE infections occurring from March to June. In addition, enrolment was suspended in South Africa during the RV season while subjects in Malawi were enrolled without interruption. A high circulation of RV was observed in Malawi as shown by the seroconversion rates in a subset of subjects in the placebo group: 40.5% of the subjects in the placebo group had seroconverted at two months post Dose 3 as opposed to 11.6% of subjects in the placebo group in South Africa.

Also, in terms of severe RV GE infections in the placebo group, the incidence of severe RV GE in Malawi was greater when compared to South Africa. Of the 61 RV GE episodes reported in Malawi, there were a total of 38 severe RV GE episodes (62.3%) and in South Africa, of the 113 RV GE episodes reported, there were a total of 32 severe RV GE episodes (28.3%). The difference could be attributed to multiple factors.

Due to the high background incidence of severe RV disease, the impact of vaccination in Africa should be substantial. The exploratory analysis performed using the Cox model showed that for every 100 infants vaccinated in this study, a total of 5 severe RV GE could be prevented. While overall efficacy estimates were lower in Malawi as compared to South Africa, the impact of vaccination may be greater in Malawi due to the even higher background incidence of severe infection. The exploratory analysis performed using the Cox model showed that a total of 6.6 severe RV GE episodes could be prevented by vaccinating 100 infants in Malawi as compared to 4.2 severe RV GE episodes in South Africa.

Vaccine efficacy against severe RV GE from Dose 1 up to Visit 6 was 59.2% [95% CI: 43.1%; 70.9%]. Protective efficacy following Dose 1 was also observed in other efficacy trials conducted in Latin America [Ruiz Palacios, 2006], Asia [GlaxoSmithKline Biologicals' Clinical Report Rota-028; 029; 030] and Europe [Vesikari, 2006].

Although the analyses were exploratory in nature, there was no statistical difference observed between the vaccine efficacy results of the two different vaccine regimens. Vaccine efficacy against severe RV GE was 58.7% [95% CI: 35.7%; 74.0%] with the HRV_2D schedule and was 63.7% [95% CI: 42.4%; 77.8%] with the HRV_3D schedule.

Fewer subjects in the HRV pooled group were hospitalised due to RV GE from 2 weeks post Dose 3 up to Visit 6 (0.5% versus 1.1%). Vaccine efficacy against hospitalisations due to severe RV GE was 57.5% [95% CI: 7.2%; 80.8%]. Compared to the other efficacy trials [GlaxoSmithKline Biologicals' Clinical Report Rota-028; 029; 030; Vesikari,

2006], the vaccine efficacy is lower. However, due to the higher disease burden in Africa, a higher impact of vaccination can be expected.

All cause severe GE was reported in significantly fewer subjects in the HRV pooled group compared to the placebo group from 2 weeks post Dose 2 up to Visit 6. Vaccine efficacy against all cause severe GE was 30.2% [95% CI: 15%; 42.6%].

The safety profile was similar in all 3 groups. There was no statistical difference between groups for the percentage of subjects with SAEs and AEs/SAEs leading to drop out. From Dose 1 up to Visit 6, there were a total of 126 fatal events (83 subjects (2.5%) in the HRV pooled group and 43 subjects (2.6%) in the placebo group). [redacted] There was no potential imbalance between groups for the percentage of subjects with fatalities due to "Pneumonia disease" and "Lower respiratory tract and lung infections". The number of fatal cases observed in this study must be put in perspective of the exisiting infant mortality rate in South Africa (45 deaths per 1000 live births) and Malawi (76 deaths per 1000 live births). Also, the fatal events reported seem to be in line with the mortality rate exisiting in the same geographical region [Department of Health, 1998; UNICEF, 2006].

In the subset of subjects with pre-vaccination blood samples, the anti-rotavirus seroconversion rate was 58.4% [95% CI: 51.6%; 64.9%] in the HRV pooled group and 22.5% [95% CI: 15.1%; 31.4%] in placebo group. The seroconversion rates observed in this study are similar to the results observed in earlier South African studies [Steele, 2008].

In all subjects with post-vaccination blood samples, the anti-rotavirus seropositivity rate at Visit 4 was 63.6% [95% CI: 61.6%; 65.6%] in HRV pooled group and 23.3% [95% CI: 20.8%; 25.9%] in placebo group. The high seropositivity rate in the placebo group at Visit 4 indicates early exposure to RV infection. The seropositivity rate observed at Visit 4 in Malawi was higher when compared to South Africa (40.4% in Malawi vs 16.7% in South Africa) indicating a high incidence of circulating RV during the vaccination period. There was no statistically significant difference between 2 different vaccination regimens in terms of anti-rotavirus IgA antibody GMCs at Visit 4.

Overall, the efficacy results obtained with 2 and 3 doses of HRV vaccine are promising and indicate that including this vaccine in the public health programmes in countries with high infant mortality would be of significant public health value.

10.2. Overall conclusions

Efficacy

- Two doses and three doses of GSK Biologicals' HRV vaccine were effective in preventing severe RV GE caused by the circulating wild-type RV during the period from 2 weeks post Dose 3 up to Visit 6 with a vaccine efficacy of 61.2% [95% CI: 44.0%; 73.2%]. The primary objective of this study was met.

- Two doses and three doses of GSK Biologicals' HRV vaccine were effective during the period from 2 weeks post Dose 3 up to Visit 6 in protecting infants against:
  - Severe RV GE caused by the circulating G1 wild type with a vaccine efficacy of 64.1% [95% CI: 29.9%; 82.0%].
  - Severe RV GE caused by the non-G1 types with a vaccine efficacy of 59.7% [95% CI: 37.1%; 74.4%].
  - Hospitalisation due to RV GE with a vaccine efficacy of 57.5% [95% CI: 7.2%; 80.8%].
  - Any RV GE caused by the circulating G1 wild type with a vaccine efficacy of 53.4% [95% CI: 42.1%; 62.6%].
  - Any RV GE caused by the non-G1 types with a vaccine efficacy of 43.5% [95% CI: 25.1%; 57.3%].
- Although this study was not adequately powered to evaluate the difference between two regimens, there was no statistically significant difference between the 2 Dose and 3 Dose regimens.
- During the period starting from Dose 1 up to Visit 6, vaccine efficacy against severe RV GE caused by the circulating wild type RV was 59.2% [95% CI: 43.1%; 70.9%].
- Vaccine efficacy against all cause severe GE reported during the period from 2 weeks post Dose 3 up to Visit 6 was 30.2% [95% CI: 15%; 42.6%].

Safety

- There was no evidence of a clinically meaningful difference between the HRV vaccine group and the placebo group for SAEs reported from Dose 1 up to Visit 6 including SAEs leading to drop out.

Immunogenicity

- The anti-rotavirus IgA antibody seropositivity rate at one month post Dose 3 of HRV vaccine was 63.6% [95% CI: 61.6%; 65.6%] in the HRV pooled group. In a subset of subjects with pre-vaccination blood samples and seronegative prior to Dose 1, the anti-rotavirus IgA seroconversion rate was 58.4% [95% CI: 51.6%; 64.9%] in the HRV pooled group at one month post Dose 3 of HRV vaccine.
- There was no significant difference between the two different HRV vaccine regimens.

11. SUPPLEMENTS

Supplement 1 Number of subjects by center (Total vaccinated cohort)

	HRV_2D	HRV_3D	HRV_POOL	Placebo	Total	
Center	n	n	n	n	n	%
[redacted]	98	99	197	99	296	6.0
	35	34	69	33	102	2.1
	55	56	111	55	166	3.4
	106	107	213	107	320	6.5
	35	34	69	34	103	2.1
	49	47	96	47	143	2.9
	117	117	234	114	348	7.0
	218	218	436	218	654	13.2
	85	85	170	85	255	5.2
	64	63	127	62	189	3.8
	143	146	289	144	433	8.8
	52	53	105	52	157	3.2
	223	226	449	221	670	13.6
	123	127	250	124	374	7.6
	128	123	251	129	380	7.7
	116	116	232	117	349	7.1
All	1647	1651	3298	1641	4939	100

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 x 100
Center = GSK Biologicals assigned center number

Supplement 2 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion (Cohort 1 South Africa cohort)

	Total			HRV_2D		HRV_3D		Placebo	
Title	n	s	%	n	s	n	s	n	s
Total cohort	1828								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1							
Total vaccinated cohort	1827		100	610		612		605	
Randomisation code broken at the investigator site (code 1060)	4	4		1	1	3	3	0	0
Study vaccine dose not administered according to protocol (code 1070)	20	22		10	10	5	6	5	6
ATP cohort for safety	1803		98.7	599		604		600	
Protocol violation (inclusion/exclusion criteria) (code 2010)	10	10		4	4	3	3	3	3
Initially seropositive (code 2020)	25	26		6	7	8	8	11	11
Initially unknown antibody status (code 2020)	126	128		44	45	40	41	42	42
Initially seropositive or initially unknown antibody status (code 2020)	151	154		50	52	48	49	53	53
Administration of any medication forbidden by the protocol (code 2040)	3	5		0	1	1	1	2	3
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	57	72		15	20	22	24	20	28
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	24	31		6	7	10	10	8	14
Essential serological data missing (code 2100)	253	304		77	99	96	111	80	94
ATP cohort for immunogenicity	1305		71.4	447		424		434	
Additional Initially unknown antibody status	1100	1100		377	377	358	358	365	365
ATP cohort for seroconversion	205		11.2	70		66		69	

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

Supplement 3 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion (Cohort 2 South Africa)

	Total			HRV_2D		HRV_3D		Placebo	
Title	n	s	%	n	s	n	s	n	s
Total cohort	1340								
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1							
Total vaccinated cohort	1339		100	447		447		445	
Randomisation code broken at the investigator site (code 1060)	1	1		0	0	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	3	3		1	1	0	0	2	2
ATP cohort for safety	1335		99.7	446		446		443	
Protocol violation (inclusion/exclusion criteria) (code 2010)	8	8		1	1	5	5	2	2
Administration of any medication forbidden by the protocol (code 2040)	6	6		4	4	0	0	2	2
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	46	46		18	18	11	11	17	17
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	10	11		5	5	1	2	4	4
Essential serological data missing (code 2100)	111	115		36	36	36	38	39	41
ATP cohort for immunogenicity	1154		86.2	382		393		379	
Additional Initially unknown antibody status	1154	1154		382	382	393	393	379	379
ATP cohort for seroconversion	0		0.0	0		0		0	

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

Supplement 4 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion (South Africa)

	Total			HRV_2D		HRV_3D		Placebo	
Title	n	s	%	n	s	n	s	n	s
Total cohort	3168								
Study vaccine dose not administrated but subject number allocated (code 1030)	2	2							
Total vaccinated cohort	3166		100	1057		1059		1050	
Randomisation code broken at the investigator site (code 1060)	5	5		1	1	4	4	0	0
Study vaccine dose not administered according to protocol (code 1070)	23	25		11	11	5	6	7	8
ATP cohort for safety	3138		99.1	1045		1050		1043	
Protocol violation (inclusion/exclusion criteria) (code 2010)	18	18		5	5	8	8	5	5
Initially seropositive (code 2020)	25	26		6	7	8	8	11	11
Initially unknown antibody status (code 2020)	126	128		44	45	40	41	42	42
Initially seropositive or initially unknown antibody status (code 2020)	151	154		50	52	48	49	53	53
Administration of any medication forbidden by the protocol (code 2040)	9	11		4	5	1	1	4	5
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	103	118		33	38	33	35	37	45
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	34	42		11	12	11	12	12	18
Essential serological data missing (code 2100)	364	419		113	135	132	149	119	135
ATP cohort for immunogenicity	2459		77.7	829		817		813	
Additional Initially unknown antibody status	2254	2254		759	759	751	751	744	744
ATP cohort for seroconversion	205		6.5	70		66		69	

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

Supplement 5 Deviations from specifications for age and intervals between study visits - Cohort 1 South Africa (Total vaccinated cohort)

		Age Dose1	BL 1-Dose1	Dose1-Dose2		Dose2-Dose3		Dose3-BL 2	
Group		Protocol	Protocol	Protocol	Adapted	Protocol	Adapted	Protocol	Adapted
		from 5 to 10 weeks	from 0 to 0 days	from 28 to 48 days	from 21 to 48 days	from 28 to 48 days	from 21 to 48 days	from 30 to 48 days	from 21 to 48 days
HRV_2D	N	610	92	579	579	560	560	526	526
	n	4	5	18	14	21	10	50	8
	%	0.7	5.4	3.1	2.4	3.8	1.8	9.5	1.5
	range	3 to 10	0 to 6	19 to 91	19 to 91	26 to 72	26 to 72	-6 to 62	-6 to 62
HRV_3D	N	612	98	568	568	554	554	517	517
	n	3	7	16	14	24	15	50	10
	%	0.5	7.1	2.8	2.5	4.3	2.7	9.7	1.9
	range	4 to 11	0 to 7	22 to 78	22 to 78	14 to 84	14 to 84	27 to 78	27 to 78
HRV_POOL	N	1222	190	1147	1147	1114	1114	1043	1043
	n	7	12	34	28	45	25	100	18
	%	0.6	6.3	3.0	2.4	4.0	2.2	9.6	1.7
	range	3 to 11	0 to 7	19 to 91	19 to 91	14 to 84	14 to 84	-6 to 78	-6 to 78
Placebo	N	605	92	576	576	559	559	523	523
	n	3	5	21	18	21	12	68	14
	%	0.5	5.4	3.6	3.1	3.8	2.1	13.0	2.7
	range	2 to 10	0 to 3	22 to 91	22 to 91	11 to 82	11 to 82	4 to 97	4 to 97

Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results in cohort 1
n (%) = number (percentage) of subjects with results outside the interval in cohort 1
range = minimum-maximum for age and intervals
BL 1=Blood sample done at visit 1
BL 2=Blood sample done at visit 4

Supplement 6 Deviations from specifications for age and intervals between study visits – Cohort 2 South Africa and Malawi cohort (Total vaccinated cohort)

		Age at Dose1	BL 1-Dose1	Dose1-Dose2		Dose2-Dose3		Dose3-BL 2	
Group		Protocol	Protocol	Protocol	Adapted	Protocol	Adapted	Protocol	Adapted
		from 5 to 10 weeks	from 0 to 0 days	from 28 to 48 days	from 21 to 48 days	from 28 to 48 days	from 21 to 48 days	from 30 to 48 days	from 21 to 48 days
HRV_2D	N	1037	57	982	982	963	963	945	945
	n	2	0	23	23	22	21	30	29
	%	0.2	0.0	2.3	2.3	2.3	2.2	3.2	3.1
	range	4 to 11	0 to 0	28 to 84	28 to 84	20 to 71	20 to 71	28 to 126	28 to 126
HRV_3D	N	1039	78	965	965	942	942	919	919
	n	6	0	23	22	19	17	22	21
	%	0.6	0.0	2.4	2.3	2.0	1.8	2.4	2.3
	range	4 to 11	0 to 0	27 to 112	27 to 112	20 to 77	20 to 77	29 to 191	29 to 191
HRV_POOL	N	2076	135	1947	1947	1905	1905	1864	1864
	n	8	0	46	45	41	38	52	50
	%	0.4	0.0	2.4	2.3	2.2	2.0	2.8	2.7
	range	4 to 11	0 to 0	27 to 112	27 to 112	20 to 77	20 to 77	28 to 191	28 to 191
Placebo	N	1036	71	965	965	935	935	904	904
	n	2	0	23	22	22	22	24	21
	%	0.2	0.0	2.4	2.3	2.4	2.4	2.7	2.3
	range	4 to 11	0 to 0	22 to 80	22 to 80	28 to 82	28 to 82	27 to 139	27 to 139

Adapted = interval used for defining the ATP cohorts for immunogenicity
N = total number of subjects with available results in cohort 2 in South Africa and Malawi cohort
n (%) = number / percentage of subjects with results outside the interval
range = minimum-maximum for age and intervals
BL 1=Blood sample done at visit 1
BL 2=Blood sample done at visit 4

Supplement 7 Summary of demographic characteristics (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.3	-	6.4	-	6.4	-	6.4	-	6.4	-
	SD	0.92	-	0.98	-	0.95	-	0.97	-	0.96	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	3	-	4	-	3	-	2	-	2	-
	Maximum	11	-	11	-	11	-	11	-	11	-
Age at dose 2 (weeks)	Mean	11.2	-	11.3	-	11.3	-	11.3	-	11.3	-
	SD	1.22	-	1.29	-	1.26	-	1.26	-	1.26	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	7	-	8	-	7	-	9	-	7	-
	Maximum	20	-	21	-	21	-	19	-	21	-
	Unknown	86	-	118	-	204	-	100	-	304	-
Age at dose 3 (weeks)	Mean	16.2	-	16.3	-	16.2	-	16.3	-	16.3	-
	SD	1.44	-	1.49	-	1.47	-	1.51	-	1.48	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	12	-	13	-	12	-	12	-	12	-
	Maximum	25	-	26	-	26	-	25	-	26	-
	Unknown	124	-	155	-	279	-	145	-	424	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	10.9	-	10.7	-	10.8	-	10.7	-	10.8	-
	SD	2.71	-	2.98	-	2.85	-	2.87	-	2.86	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	1	-	1	-	1	-	1	-	1	-
	Maximum	19	-	28	-	28	-	19	-	28	-
	Unknown	0	-	1	-	1	-	0	-	1	-
Gender	Female	811	49.2	839	50.8	1650	50.0	800	48.8	2450	49.6
	Male	836	50.8	812	49.2	1648	50.0	841	51.2	2489	50.4
Race	African heritage / African American	1602	97.3	1602	97.0	3204	97.1	1592	97.0	4796	97.1
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific Islande	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	2	0.1	3	0.2	5	0.2	1	0.1	6	0.1
	Other	43	2.6	46	2.8	89	2.7	48	2.9	137	2.8
Height at visit 1(cm)	Mean	54.3	-	54.3	-	54.3	-	54.3	-	54.3	-
	SD	3.00	-	3.09	-	3.05	-	3.17	-	3.09	-
	Median	54.0	-	55.0	-	54.0	-	55.0	-	54.0	-
	Unknown	0	-	0	-	0	-	1	-	1	-

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Weight at visit 1 (kg)	Mean	4.9	-	4.9	-	4.9	-	4.9	-	4.9	-
	SD	0.70	-	0.71	-	0.70	-	0.70	-	0.70	-
	Median	4.9	-	4.9	-	4.9	-	4.9	-	4.9	-
BMI at visit 1 (kg/m²)	Mean	16.6	-	16.6	-	16.6	-	16.7	-	16.6	-
	SD	2.35	-	2.38	-	2.37	-	2.44	-	2.39	-
	Median	16.4	-	16.3	-	16.4	-	16.5	-	16.4	-
	Unknown	0	-	0	-	0	-	1	-	1	-

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

Supplement 8 Summary of demographic characteristics - South Africa Cohort 1 (Total vaccinated cohort)

		HRV_2D N = 610		HRV_3D N = 612		HRV_POOL N = 1222		Placebo N = 605		Total N = 1827	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.2	-	6.4	-	6.3	-	6.3	-	6.3	-
	SD	0.96	-	1.01	-	0.99	-	0.98	-	0.99	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	3	-	4	-	3	-	2	-	2	-
	Maximum	10	-	11	-	11	-	10	-	11	-
Age at dose 2 (weeks)	Mean	11.1	-	11.2	-	11.1	-	11.2	-	11.2	-
	SD	1.33	-	1.31	-	1.32	-	1.35	-	1.33	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	7	-	8	-	7	-	9	-	7	-
	Maximum	20	-	17	-	20	-	19	-	20	-
	Unknown	31	-	44	-	75	-	29	-	104	-
Age at dose 3 (weeks)	Mean	15.9	-	16.2	-	16.0	-	16.1	-	16.0	-
	SD	1.59	-	1.57	-	1.59	-	1.61	-	1.59	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	12	-	13	-	12	-	12	-	12	-
	Maximum	24	-	25	-	25	-	25	-	25	-
	Unknown	50	-	58	-	108	-	45	-	153	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	10.8	-	10.7	-	10.7	-	10.8	-	10.8	-
	SD	2.81	-	3.02	-	2.92	-	2.63	-	2.82	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	1	-	1	-	1	-	1	-	1	-
	Maximum	19	-	28	-	28	-	19	-	28	-
	Unknown	0	-	1	-	1	-	0	-	1	-
Gender	Female	317	52.0	311	50.8	628	51.4	292	48.3	920	50.4
	Male	293	48.0	301	49.2	594	48.6	313	51.7	907	49.6
Race	African heritage / African American	609	99.8	608	99.3	1217	99.6	602	99.5	1819	99.6
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific Islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	1	0.2	3	0.5	4	0.3	1	0.2	5	0.3
	Other - coloured / mixed	0	0.0	1	0.2	1	0.1	2	0.3	3	0.2
Height at visit 1(cm)	Mean	55.6	-	55.7	-	55.6	-	55.5	-	55.6	-
	Sd	2.83	-	2.79	-	2.81	-	2.77	-	2.80	-
	Median	56.0	-	56.0	-	56.0	-	56.0	-	56.0	-
	Unknown	0	-	0	-	0	-	1	-	1	-

		HRV_2D N = 610		HRV_3D N = 612		HRV_POOL N = 1222		Placebo N = 605		Total N = 1827	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Weight at visit 1 (kg)	Mean	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-
	Sd	0.68	-	0.68	-	0.68	-	0.69	-	0.68	-
	Median	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-
BMI at visit 1 (kg/m²)	Mean	15.5	-	15.5	-	15.5	-	15.5	-	15.5	-
	Sd	1.99	-	2.02	-	2.00	-	2.00	-	2.00	-
	Median	15.4	-	15.4	-	15.4	-	15.4	-	15.4	-
	Unknown	0	-	0	-	0	-	1	-	1	-

N = total number of subjects in South Africa cohort 1
n (%) = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 9 Summary of demographic characteristics - South Africa Cohort 2 (Total vaccinated cohort)

		HRV_2D N = 447		HRV_3D N = 447		HRV_POOL N = 894		Placebo N = 445		Total N = 1339	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.2	-	6.2	-	6.2	-	6.2	-	6.2	-
	SD	0.89	-	0.92	-	0.91	-	0.92	-	0.91	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	4	-	4	-	4	-	4	-	4	-
	Maximum	10	-	10	-	10	-	10	-	10	-
Age at dose 2 (weeks)	Mean	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	SD	1.09	-	1.09	-	1.09	-	1.19	-	1.12	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	9	-	8	-	8	-	9	-	8	-
	Maximum	15	-	15	-	15	-	15	-	15	-
	Unknown	19	-	13	-	32	-	16	-	48	-
Age at dose 3 (weeks)	Mean	15.9	-	15.8	-	15.9	-	16.0	-	15.9	-
	SD	1.31	-	1.31	-	1.31	-	1.42	-	1.35	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	13	-	13	-	13	-	13	-	13	-
	Maximum	20	-	21	-	21	-	23	-	23	-
	Unknown	25	-	21	-	46	-	22	-	68	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Sd	2.25	-	2.14	-	2.19	-	2.29	-	2.22	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	1	-	2	-	1	-	1	-	1	-
	Maximum	14	-	13	-	14	-	13	-	14	-
Gender	Female	229	51.2	216	48.3	445	49.8	215	48.3	660	49.3
	Male	218	48.8	231	51.7	449	50.2	230	51.7	679	50.7
Race	African heritage / african american	403	90.2	402	89.9	805	90.0	399	89.7	1204	89.9
	American indian or alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - central/south asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - east asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - south east asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - arabic / north african heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - caucasian / european heritage	1	0.2	0	0.0	1	0.1	0	0.0	1	0.1
	Other - coloured / mixed	43	9.6	45	10.1	88	9.8	46	10.3	134	10.0
Height (cm)	Mean	54.5	-	54.6	-	54.6	-	54.7	-	54.6	-
	Sd	2.58	-	2.67	-	2.62	-	3.08	-	2.78	-
	Median	54.0	-	55.0	-	55.0	-	55.0	-	55.0	-
Weight (kg)	Mean	4.8	-	4.8	-	4.8	-	4.9	-	4.8	-
	Sd	0.70	-	0.69	-	0.69	-	0.67	-	0.68	-
	Median	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-

		HRV_2D N = 447		HRV_3D N = 447		HRV_POOL N = 894		Placebo N = 445		Total N = 1339	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
BMI (kg/m²)	Mean	16.1	-	16.2	-	16.2	-	16.3	-	16.2	-
	Sd	1.92	-	1.87	-	1.89	-	2.42	-	2.09	-
	Median	16.0	-	16.1	-	16.1	-	16.2	-	16.1	-

N = total number of subjects in South Africa Cohort 2
n (%) = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 10 Summary of demographic characteristics - South Africa (Total vaccinated cohort)

		HRV_2D N = 1057		HRV_3D N = 1059		HRV_POOL N = 2116		Placebo N = 1050		Total N = 3166	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.2	-	6.3	-	6.3	-	6.3	-	6.3	-
	SD	0.93	-	0.98	-	0.96	-	0.96	-	0.96	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	3	-	4	-	3	-	2	-	2	-
	Maximum	10	-	11	-	11	-	10	-	11	-
Age at dose 2 (weeks)	Mean	11.0	-	11.1	-	11.1	-	11.1	-	11.1	-
	SD	1.23	-	1.22	-	1.23	-	1.28	-	1.25	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	7	-	8	-	7	-	9	-	7	-
	Maximum	20	-	17	-	20	-	19	-	20	-
	Unknown	50	-	57	-	107	-	45	-	152	-
Age at dose 3 (weeks)	Mean	15.9	-	16.0	-	16.0	-	16.0	-	16.0	-
	SD	1.47	-	1.47	-	1.48	-	1.53	-	1.49	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	12	-	13	-	12	-	12	-	12	-
	Maximum	24	-	25	-	25	-	25	-	25	-
	Unknown	75	-	79	-	154	-	67	-	221	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	10.9	-	10.8	-	10.9	-	10.9	-	10.9	-
	SD	2.59	-	2.69	-	2.64	-	2.49	-	2.59	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	1	-	1	-	1	-	1	-	1	-
	Maximum	19	-	28	-	28	-	19	-	28	-
	Unknown	0	-	1	-	1	-	0	-	1	-
Gender	Female	546	51.7	527	49.8	1073	50.7	507	48.3	1580	49.9
	Male	511	48.3	532	50.2	1043	49.3	543	51.7	1586	50.1
Race	African heritage / African American	1012	95.7	1010	95.4	2022	95.6	1001	95.3	3023	95.5
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific Islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	2	0.2	3	0.3	5	0.2	1	0.1	6	0.2
	Other - coloured / mixed	43	4.1	46	4.3	89	4.2	48	4.6	137	4.3
Height at visit 1(cm)	Mean	55.1	-	55.2	-	55.2	-	55.2	-	55.2	-
	SD	2.78	-	2.79	-	2.78	-	2.94	-	2.84	-
	Median	55.0	-	55.0	-	55.0	-	55.0	-	55.0	-
	Unknown	0	-	0	-	0	-	1	-	1	-

		HRV_2D N = 1057		HRV_3D N = 1059		HRV_POOL N = 2116		Placebo N = 1050		Total N = 3166	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Weight at visit 1 (kg)	Mean	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-
	SD	0.69	-	0.68	-	0.68	-	0.68	-	0.68	-
	Median	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-
BMI at visit 1 (kg/m²)	Mean	15.8	-	15.8	-	15.8	-	15.9	-	15.8	-
	SD	1.98	-	1.98	-	1.98	-	2.22	-	2.06	-
	Median	15.7	-	15.7	-	15.7	-	15.8	-	15.7	-
	Unknown	0	-	0	-	0	-	1	-	1	-

N = total number of subjects in given South Africa
n (%) = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 11 Summary of demographic characteristics - Malawi (Total vaccinated cohort)

		HRV_2D N = 590		HRV_3D N = 592		HRV_POOL N = 1182		Placebo N = 591		Total N = 1773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.5	-	6.6	-	6.5	-	6.5	-	6.5	-
	SD	0.87	-	0.96	-	0.92	-	0.97	-	0.94	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	5	-	4	-	4	-	5	-	4	-
	Maximum	11	-	11	-	11	-	11	-	11	-
Age at dose 2 (weeks)	Mean	11.6	-	11.8	-	11.7	-	11.6	-	11.7	-
	SD	1.09	-	1.31	-	1.21	-	1.16	-	1.19	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	10	-	9	-	9	-	9	-	9	-
	Maximum	19	-	21	-	21	-	19	-	21	-
	Unknown	36	-	61	-	97	-	55	-	152	-
Age at dose 3 (weeks)	Mean	16.7	-	16.8	-	16.8	-	16.8	-	16.8	-
	SD	1.21	-	1.37	-	1.29	-	1.34	-	1.31	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	14	-	14	-	14	-	14	-	14	-
	Maximum	25	-	26	-	26	-	24	-	26	-
	Unknown	49	-	76	-	125	-	78	-	203	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	10.9	-	10.6	-	10.7	-	10.5	-	10.7	-
	SD	2.92	-	3.44	-	3.19	-	3.44	-	3.28	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	1	-	1	-	1	-	1	-	1	-
	Maximum	16	-	16	-	16	-	17	-	17	-
Gender	Female	265	44.9	312	52.7	577	48.8	293	49.6	870	49.1
	Male	325	55.1	280	47.3	605	51.2	298	50.4	903	50.9
Race	African heritage / African American	590	100	592	100	1182	100	591	100	1773	100
	American Indian or Alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific Islande	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Other	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Height at visit 1(cm)	Mean	52.9	-	52.8	-	52.8	-	52.8	-	52.8	-
	SD	2.83	-	2.99	-	2.91	-	3.01	-	2.94	-
	Median	53.0	-	53.0	-	53.0	-	53.0	-	53.0	-
Weight at visit 1 (kg)	Mean	5.1	-	5.0	-	5.0	-	5.0	-	5.0	-
	SD	0.69	-	0.74	-	0.71	-	0.70	-	0.71	-
	Median	5.1	-	5.0	-	5.1	-	5.0	-	5.1	-

		HRV_2D N = 590		HRV_3D N = 592		HRV_POOL N = 1182		Placebo N = 591		Total N = 1773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
BMI at visit 1 (kg/m²)	Mean	18.1	-	18.0	-	18.1	-	18.0	-	18.1	-
	SD	2.21	-	2.39	-	2.30	-	2.19	-	2.26	-
	Median	18.1	-	17.9	-	18.1	-	17.8	-	17.9	-

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

Supplement 12 Number of days between the 3 doses of HRV vaccine/placebo (Total vaccinated cohort)

		HRV_2D	HRV_3D	HRV_POOL	Placebo	Total
Characteristics	Parameters or Categories	Value or n	Value or n	Value or n	Value or n	Value or n
Number of days between dose 1 and dose 2	N	1561	1533	3094	1541	4635
	Mean	34.7	34.9	34.8	34.8	34.8
	std	5.54	5.93	5.74	5.85	5.77
	Min	19	22	19	22	19
	Q1	31	32	31	31	31
	Median	35	35	35	35	35
	Q3	36	36	36	36	36
	Max	91	112	112	91	112
Number of days between dose 2 and dose 3	N	1523	1496	3019	1494	4513
	Mean	34.8	34.9	34.9	35.1	35.0
	std	4.81	5.12	4.96	5.32	5.09
	Min	20	14	14	11	11
	Q1	33	33	33	33	33
	Median	35	35	35	35	35
	Q3	36	36	36	36	36
	Max	72	84	84	82	84

N for number of days between dose1 and dose2: N = number of subject with dose 1 and dose 2 administered
N for number of days between dose2 and dose3: N = number of subject with dose 2 and dose 3 administered
n = number of subject number in a given category; Value = value of the considered parameter
Q1=25th percentile, Q3=75th percentile; SD= standard deviation

Supplement 13 Increase in height (cm) and weight (kg) from Visit 1 to Visits 4 and 6 (Total vaccinated cohort)

			HRV_2D	HRV_3D	HRV_POOL	Placebo	Total
Characteristics		Parameters or Categories	Value or n	Value or n	Value or n	Value or n	Value or n
Visit 4	Increase in Height (cm) from visit 1	N	1507	1475	2982	1469	4451
		mean	8.5	8.5	8.5	8.6	8.5
		SD	2.56	2.60	2.58	2.80	2.65
		median	8.0	8.0	8.0	8.0	8.0
		missing	140	176	316	172	488
	Increase in Weight (kg) from visit 1	N	1508	1477	2985	1471	4456
		mean	2.4	2.4	2.4	2.4	2.4
		SD	0.72	0.75	0.74	0.73	0.73
		median	2.4	2.4	2.4	2.3	2.4
		missing	139	174	313	170	483
Visit 6	Increase in Height (cm) from visit 1	N	1414	1379	2793	1389	4182
		mean	17.7	17.6	17.6	17.7	17.7
		SD	3.47	3.37	3.42	3.44	3.43
		median	18.0	18.0	18.0	18.0	18.0
		missing	233	272	505	252	757
	Increase in Weight (kg) from visit 1	N	1417	1383	2800	1390	4190
		mean	4.4	4.4	4.4	4.3	4.3
		SD	1.13	1.12	1.12	1.13	1.12
		median	4.2	4.3	4.3	4.3	4.3
		missing	230	268	498	251	749

N = number of subjects for whom height and weight is recorded at their corresponding visit
n = number of subject number in a given category
Value = value of the considered parameter
SD = Standard deviation

Supplement 14 Increase in height (cm) and weight (kg) from Visit 1 to Visits 4 and 6 by country (Total vaccinated cohort)

			HRV_2D	HRV_3D	HRV_POOL	Placebo	Total
Country	Characteristics	Parameters or Categories	Value or n	Value or n	Value or n	Value or n	Value or n
Malawi							
Visit 4	Increase in Height (cm) from visit 1	N	537	513	1050	502	1552
		mean	8.7	8.4	8.6	8.7	8.6
		Sd	2.49	2.56	2.53	2.50	2.52
		median	9.0	8.0	9.0	8.0	9.0
		missing	53	79	132	89	221
	Increase in Weight (kg) from visit 1	N	537	513	1050	502	1552
		mean	2.3	2.3	2.3	2.3	2.3
		Sd	0.67	0.67	0.67	0.61	0.65
		median	2.3	2.3	2.3	2.3	2.3
		missing	53	79	132	89	221
Visit 6	Increase in Height (cm) from visit 1	N	502	479	981	470	1451
		mean	18.3	17.8	18.1	17.9	18.0
		Sd	3.32	3.23	3.29	3.06	3.22
		median	18.0	18.0	18.0	18.0	18.0
		missing	88	113	201	121	322
	Increase in Weight (kg) from visit 1	N	502	479	981	470	1451
		mean	4.0	3.9	3.9	4.0	3.9
		Sd	0.90	0.97	0.93	0.93	0.93
		median	3.9	3.9	3.9	3.9	3.9
		missing	88	113	201	121	322
South Africa							
Visit 4	Increase in Height (cm) from visit 1	N	970	962	1932	967	2899
		mean	8.4	8.5	8.5	8.5	8.5
		Sd	2.59	2.62	2.60	2.94	2.72
		median	8.0	8.0	8.0	8.0	8.0
		missing	87	97	184	83	267
	Increase in Weight (kg) from visit 1	N	971	964	1935	969	2904
		mean	2.4	2.5	2.5	2.4	2.5
		Sd	0.75	0.78	0.77	0.78	0.77
		median	2.4	2.4	2.4	2.4	2.4
		missing	86	95	181	81	262
Visit 6	Increase in Height (cm) from visit 1	N	912	900	1812	919	2731
		mean	17.4	17.5	17.4	17.6	17.5
		Sd	3.51	3.44	3.48	3.62	3.52
		median	17.0	17.0	17.0	18.0	17.0
		missing	145	159	304	131	435
	Increase in Weight (kg) from visit 1	N	915	904	1819	920	2739
		mean	4.6	4.6	4.6	4.5	4.6
		Sd	1.18	1.13	1.15	1.17	1.16
		median	4.5	4.5	4.5	4.5	4.5
		missing	142	155	297	130	427

N = number of subjects for whom height and weight is recorded at their corresponding visit
n = number of subject number in a given category
Value = value of the considered parameter
SD = Standard deviation

Supplement 15 Increase in height (cm) and weight (kg) from Visit 1 to Visits 4 and 6 by cohort - South Africa (Total vaccinated cohort)

			HRV_2D	HRV_3D	HRV_POOL	Placebo	Total
	Characteristics	Parameters or Categories	Value or n	Value or n	Value or n	Value or n	Value or n
Cohort 1							
Visit 4	Increase in Height (cm) from visit 1	N	550	541	1091	548	1639
		mean	8.2	8.2	8.2	8.2	8.2
		Sd	2.70	2.68	2.69	2.73	2.70
		median	8.0	8.0	8.0	8.0	8.0
		missing	60	71	131	57	188
	Increase in Weight (kg) from visit 1	N	550	543	1093	549	1642
		mean	2.5	2.5	2.5	2.4	2.5
		Sd	0.75	0.80	0.78	0.79	0.78
		median	2.4	2.4	2.4	2.3	2.4
		missing	60	69	129	56	185
Visit 6	Increase in Height (cm) from visit 1	N	513	503	1016	525	1541
		mean	17.0	17.00	17.0	17.4	17.1
		Sd	3.65	3.45	3.55	3.53	3.55
		median	17.0	17.0	17.0	17.0	17.0
		missing	97	109	206	80	286
	Increase in Weight (kg) from visit 1	N	516	506	1022	526	1548
		mean	4.6	4.6	4.6	4.56	4.6
		Sd	1.21	1.15	1.18	1.11	1.16
		median	4.5	4.4	4.5	4.5	4.5
		missing	94	106	200	79	279
Cohort 2							
Visit 4	Increase in Height (cm) from visit 1	N	420	421	841	419	1260
		mean	8.7	8.9	8.8	8.9	8.9
		Sd	2.42	2.48	2.45	3.16	2.71
		median	9.0	9.0	9.0	8.0	9.0
		missing	27	26	53	26	79
	Increase in Weight (kg) from visit 1	N	421	421	842	420	1262
		mean	2.4	2.5	2.5	2.4	2.5
		Sd	0.75	0.75	0.75	0.77	0.76
		median	2.4	2.4	2.4	2.4	2.4
		missing	26	26	52	25	77
Visit 6	Increase in Height (cm) from visit 1	N	399	397	796	394	1190
		mean	17.9	18.1	18.0	17.8	18.0
		Sd	3.25	3.33	3.29	3.71	3.44
		median	18.0	18.0	18.0	18.0	18.0
		missing	48	50	98	51	149
	Increase in Weight (kg) from visit 1	N	399	398	797	394	1191
		mean	4.6	4.6	4.6	4.5	4.6
		Sd	1.13	1.11	1.12	1.24	1.16
		median	4.5	4.5	4.5	4.4	4.5
		missing	48	49	97	51	148

N = number of subjects for whom height and weight is recorded at their corresponding visit
n = number of subject number in a given category
Value = value of the considered parameter
SD = Standard deviation

Supplement 16 Summary of malnutrition (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
visit 1	Yes	22	1.3	21	1.3	43	1.3	21	1.3	64	1.3
	No	1625	98.7	1630	98.7	3255	98.7	1620	98.7	4875	98.7
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
visit 4	Yes	12	0.8	20	1.4	32	1.1	9	0.6	41	0.9
	No	1496	99.2	1457	98.6	2953	98.9	1462	99.4	4415	99.1
	Missing	139	-	174	-	313	-	170	-	483	-
visit 6	Yes	18	1.3	17	1.2	35	1.3	13	0.9	48	1.1
	No	1399	98.7	1366	98.8	2765	98.8	1377	99.1	4142	98.9
	Missing	230	-	268	-	498	-	251	-	749	-

N = total number of subjects
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 17 Summary of malnutrition (Total vaccinated cohort, South Africa)

		HRV_2D N = 1057		HRV_3D N = 1059		HRV_POOL N = 2116		Placebo N = 1050		Total N = 3166	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
visit 1	Yes	11	1.0	11	1.0	22	1.0	12	1.1	34	1.1
	No	1046	99.0	1048	99.0	2094	99.0	1038	98.9	3132	98.9
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
visit 4	Yes	6	0.6	8	0.8	14	0.7	7	0.7	21	0.7
	No	965	99.4	956	99.2	1921	99.3	962	99.3	2883	99.3
	Missing	86	-	95	-	181	-	81	-	262	-
visit 6	Yes	8	0.9	8	0.9	16	0.9	7	0.8	23	0.8
	No	907	99.1	896	99.1	1803	99.1	913	99.2	2716	99.2
	Missing	142	-	155	-	297	-	130	-	427	-

N = total number of subjects numbering South Africa
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 18 Summary of malnutrition (Total vaccinated cohort, Malawi)

		HRV_2D N = 590		HRV_3D N = 592		HRV_POOL N = 1182		Placebo N = 591		Total N = 1773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
visit 1	Yes	11	1.9	10	1.7	21	1.8	9	1.5	30	1.7
	No	579	98.1	582	98.3	1161	98.2	582	98.5	1743	98.3
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
visit 4	Yes	6	1.1	12	2.3	18	1.7	2	0.4	20	1.3
	No	531	98.9	501	97.7	1032	98.3	500	99.6	1532	98.7
	Missing	53	-	79	-	132	-	89	-	221	-
visit 6	Yes	10	2.0	9	1.9	19	1.9	6	1.3	25	1.7
	No	492	98.0	470	98.1	962	98.1	464	98.7	1426	98.3
	Missing	88	-	113	-	201	-	121	-	322	-

N = total number of subjects in Malawi
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 19 Summary of HIV tests and results performed during the study (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Informed consent signed?	Yes	501	30.4	534	32.3	1035	31.4	516	31.4	1551	31.4
	No	1146	69.6	1117	67.7	2263	68.6	1125	68.6	3388	68.6
		HRV_2D N = 501		HRV_3D N = 534		HRV_POOL N = 1035		Placebo N = 516		Total N = 1551	
HIV test result	Unknown	0	0.0	4	0.7	4	0.4	3	0.6	7	0.5
	ELISA Negative	387	77.2	396	74.2	783	75.7	374	72.5	1157	74.6
	ELISA unknown PCR negative	36	7.2	34	6.4	70	6.8	49	9.5	119	7.7
	ELISA Positive PCR Negative	50	10.0	65	12.2	115	11.1	64	12.4	179	11.5
	ELISA Positive PCR Unknown	4	0.8	3	0.6	7	0.7	3	0.6	10	0.6
	PCR Positive	24	4.8	32	6.0	56	5.4	23	4.5	79	5.1

N= number of subject in specified cohort
n = number of subject by informed consent status
N'=number of subject signed informed consent.
n'/%=number (percentage) of subject resulting a given category
Positive= Subject has at least one positive HIV PCR test results.
Negative= Subject has negative result in HIV ELISA or PCR
Unknown= Subject for whom HIV status is unknown.

Supplement 20 Summary of HIV tests and results performed during the study – South Africa Cohort 1 (Total vaccinated cohort)

		HRV_2D N = 610		HRV_3D N = 612		HRV_POOL N = 1222		Placebo N = 605		Total N = 1827	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Informed consent signed?	Yes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	No	610	100	612	100	1222	100	605	100	1827	100

N = number of subject in Cohort 1 South Africa
n = number of subject by informed consent status

Supplement 21 Summary of HIV tests and results performed during the study – Cohort 2 South Africa (Total vaccinated cohort)

		HRV_2D N = 447		HRV_3D N = 447		HRV_POOL N = 894		Placebo N = 445		Total N = 1339	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Informed consent signed?	Yes	234	52.3	250	55.9	484	54.1	241	54.2	725	54.1
	No	213	47.7	197	44.1	410	45.9	204	45.8	614	45.9
		HRV_2D N = 234		HRV_3D N = 250		HRV_POOL N = 484		Placebo N = 241		Total N = 725	
HIV test result	Unknown	0	0.0	1	0.4	1	0.2	1	0.4	2	0.3
	ELISA Negative	174	74.4	187	74.8	361	74.6	161	66.8	522	72.0
	ELISA unknown PCR negative	34	14.5	34	13.6	68	14.0	49	20.3	117	16.1
	ELISA Positive PCR Negative	10	4.3	12	4.8	22	4.5	16	6.6	38	5.2
	ELISA Positive PCR Unknown	1	0.4	0	0.0	1	0.2	0	0.0	1	0.1
	PCR Positive	15	6.4	16	6.4	31	6.4	14	5.8	45	6.2

N= number of subject in Cohort 2 South Africa
n = number of subject by informed consent status
N'=number of subject signed informed consent.
n' (%)=number (percentage) of subject signed informed consent by HIV test result
Positive= Subject has at least one positive HIV PCR test results.
Negative= Subject has negative result in HIV ELISA or PCR
Unknown= Subject for whom HIV status is unknown.

Supplement 22 Summary of HIV tests and results performed during the study - South Africa (Total vaccinated cohort)

		HRV_2D N = 1057		HRV_3D N = 1059		HRV_POOL N = 2116		Placebo N = 1050		Total N = 3166	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Informed consent signed?	Yes	234	22.1	250	23.6	484	22.9	241	23.0	725	22.9
	No	823	77.9	809	76.4	1632	77.1	809	77.0	2441	77.1
		HRV_2D N = 234		HRV_3D N = 250		HRV_POOL N = 484		Placebo N = 241		Total N = 725	
HIV test result	Unknown	0	0.0	1	0.4	1	0.2	1	0.4	2	0.3
	ELISA Negative	174	74.4	187	74.8	361	74.6	161	66.8	522	72.0
	ELISA unknown PCR negative	34	14.5	34	13.6	68	14.0	49	20.3	117	16.1
	ELISA Positive PCR Negative	10	4.3	12	4.8	22	4.5	16	6.6	38	5.2
	ELISA Positive PCR Unknown	1	0.4	0	0.0	1	0.2	0	0.0	1	0.1
	PCR Positive	15	6.4	16	6.4	31	6.4	14	5.8	45	6.2

N= number of subjects in South Africa
n = number of subject by informed consent status
N'=number of subject signed informed consent.
n' (%)=number (percentage) of subject signed informed consent by HIV test result
Positive= Subject has at least one positive HIV PCR test results.
Negative= Subject has negative result in HIV ELISA or PCR
Unknown= Subject for whom HIV status is unknown.

Supplement 23 Summary of HIV tests and results performed during the study - Malawi (Total vaccinated cohort)

		HRV_2D N = 590		HRV_3D N = 592		HRV_POOL N = 1182		Placebo N = 591		Total N = 1773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Informed consent signed?	Yes	267	45.3	284	48.0	551	46.6	275	46.5	826	46.6
	No	323	54.7	308	52.0	631	53.4	316	53.5	947	53.4
		HRV_2D N = 267		HRV_3D N = 284		HRV_POOL N = 551		Placebo N = 275		Total N = 826	
HIV test result	Unknown	0	0.0	3	1.1	3	0.5	2	0.7	5	0.6
	ELISA Negative	213	79.8	209	73.6	422	76.6	213	77.5	635	76.9
	ELISA unknown PCR negative	2	0.7	0	0.0	2	0.4	0	0.0	2	0.2
	ELISA Positive PCR Negative	40	15.0	53	18.7	93	16.9	48	17.5	141	17.1
	ELISA Positive PCR Unknown	3	1.1	3	1.1	6	1.1	3	1.1	9	1.1
	PCR Positive	9	3.4	16	5.6	25	4.5	9	3.3	34	4.1

N= number of subjects in Malawi
n = number of subject by informed consent status
N'=number of subject signed informed consent.
n' (%)=number (percentage) of subject signed informed consent by HIV test result
Positive= Subject has at least one positive HIV PCR test results.
Negative= Subject has negative result in HIV ELISA or PCR
Unknown= Subject for whom HIV status is unknown.

Supplement 24 Summary of demographic characteristics (ATP cohort for immunogenicity)

		HRV_2D N = 1160		HRV_3D N = 1138		HRV_POOL N = 2298		Placebo N = 1125		Total N = 3423	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at dose 1 (weeks)	Mean	6.3	-	6.4	-	6.3	-	6.3	-	6.3	-
	SD	0.90	-	0.97	-	0.94	-	0.94	-	0.94	-
	Median	6.0	-	6.0	-	6.0	-	6.0	-	6.0	-
	Minimum	5	-	5	-	5	-	5	-	5	-
	Maximum	10	-	10	-	10	-	10	-	10	-
Age at dose 2 (weeks)	Mean	11.1	-	11.2	-	11.2	-	11.2	-	11.2	-
	SD	1.06	-	1.14	-	1.10	-	1.13	-	1.11	-
	Median	11.0	-	11.0	-	11.0	-	11.0	-	11.0	-
	Minimum	9	-	9	-	9	-	9	-	9	-
	Maximum	15	-	15	-	15	-	15	-	15	-
	Unknown	1	-	0	-	1	-	3	-	4	-
Age at dose 3 (weeks)	Mean	16.0	-	16.1	-	16.1	-	16.1	-	16.1	-
	SD	1.26	-	1.29	-	1.28	-	1.29	-	1.28	-
	Median	16.0	-	16.0	-	16.0	-	16.0	-	16.0	-
	Minimum	13	-	13	-	13	-	13	-	13	-
	Maximum	21	-	21	-	21	-	21	-	21	-
	Unknown	1	-	3	-	4	-	6	-	10	-
Age at visit 6 or last contact if visit 6 is not performed (months)	Mean	11.6	-	11.6	-	11.6	-	11.6	-	11.6	-
	SD	1.12	-	1.15	-	1.13	-	1.18	-	1.15	-
	Median	12.0	-	12.0	-	12.0	-	12.0	-	12.0	-
	Minimum	4	-	4	-	4	-	4	-	4	-
	Maximum	19	-	17	-	19	-	19	-	19	-
Gender	Female	586	50.5	558	49.0	1144	49.8	537	47.7	1681	49.1
	Male	574	49.5	580	51.0	1154	50.2	588	52.3	1742	50.9
Race	African Heritage / African American	1119	96.5	1093	96.0	2212	96.3	1079	95.9	3291	96.1
	American Indian Or Alaskan Native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South east Asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Native Hawaiian or other Pacific Islande	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European heritage	2	0.2	3	0.3	5	0.2	1	0.1	6	0.2
	Other	39	3.4	42	3.7	81	3.5	45	4.0	126	3.7
Height at visit 1(cm)	Mean	54.6	-	54.6	-	54.6	-	54.6	-	54.6	-
	SD	2.89	-	2.94	-	2.91	-	3.08	-	2.97	-
	Median	55.0	-	55.0	-	55.0	-	55.0	-	55.0	-
	Unknown	0	-	0	-	0	-	1	-	1	-

		HRV_2D N = 1160		HRV_3D N = 1138		HRV_POOL N = 2298		Placebo N = 1125		Total N = 3423	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Weight at visit 1 (kg)	Mean	4.9	-	4.9	-	4.9	-	4.9	-	4.9	-
	SD	0.69	-	0.70	-	0.69	-	0.68	-	0.69	-
	Median	4.9	-	4.9	-	4.9	-	4.9	-	4.9	-
BMI at visit 1 (kg/m²)	Mean	16.4	-	16.4	-	16.4	-	16.5	-	16.5	-
	SD	2.19	-	2.29	-	2.24	-	2.39	-	2.29	-
	Median	16.3	-	16.1	-	16.2	-	16.3	-	16.2	-
	Unknown	0	-	0	-	0	-	1	-	1	-

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

Supplement 25 Summary of co-administered vaccination by dose (Total vaccinated cohort)

Dose 1										
Category	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
	n	%	n	%	n	%	n	%	n	%
Any	1644	99.8	1646	99.7	3290	99.8	1638	99.8	4928	99.8
BCG	42	2.6	44	2.7	86	2.6	40	2.4	126	2.6
DTPw-HB	1035	62.8	1038	62.9	2073	62.9	1036	63.1	3109	62.9
DTPw-HB/HIB	608	36.9	608	36.8	1216	36.9	602	36.7	1818	36.8
HIB	1034	62.8	1038	62.9	2072	62.8	1036	63.1	3108	62.9
OPV	1642	99.7	1646	99.7	3288	99.7	1638	99.8	4926	99.7
Dose 2										
	HRV_2D N = 1561		HRV_3D N = 1533		HRV_POOL N = 3094		Placebo N = 1541		Total N = 4635	
	n	%	n	%	n	%	n	%	n	%
Any	1550	99.3	1522	99.3	3072	99.3	1530	99.3	4602	99.3
BCG	16	1.0	7	0.5	23	0.7	14	0.9	37	0.8
DTP+HIB	0	0.0	1	0.1	1	0.0	0	0.0	1	0.0
DTPw-HB	974	62.4	958	62.5	1932	62.4	955	62.0	2887	62.3
DTPw-HB/HIB	576	36.9	561	36.6	1137	36.7	574	37.2	1711	36.9
HBV	0	0.0	1	0.1	1	0.0	0	0.0	1	0.0
HIB	974	62.4	958	62.5	1932	62.4	956	62.0	2888	62.3
OPV	1550	99.3	1521	99.2	3071	99.3	1530	99.3	4601	99.3
Dose 3										
	HRV_2D N = 1523		HRV_3D N = 1496		HRV_POOL N = 3019		Placebo N = 1496		Total N = 4515	
	n	%	n	%	n	%	n	%	n	%
Any	1510	99.1	1487	99.4	2997	99.3	1488	99.5	4485	99.3
BCG	7	0.5	3	0.2	10	0.3	6	0.4	16	0.4
DTPw-HB	954	62.6	939	62.8	1893	62.7	929	62.1	2822	62.5
DTPw-HB/HIB	555	36.4	548	36.6	1103	36.5	559	37.4	1662	36.8
HIB	955	62.7	939	62.8	1894	62.7	928	62.0	2822	62.5
Me	0	0.0	1	0.1	1	0.0	0	0.0	1	0.0
OPV	1510	99.1	1487	99.4	2997	99.3	1488	99.5	4485	99.3

N = number of subject having received considered study vaccine dose
n (%)=number (percentage) of subject having received the specified vaccination on the same day with considered study dose.

Supplement 26 Summary of co-administered vaccination by dose – South Africa Cohort 1 (Total vaccinated cohort)

Dose 1										
Category	HRV_2D N = 610		HRV_3D N = 612		HRV_POOL N = 1222		Placebo N = 605		Total N = 1827	
	n	%	n	%	n	%	n	%	n	%
Any	609	99.8	608	99.3	1217	99.6	602	99.5	1819	99.6
BCG	1	0.2	1	0.2	2	0.2	1	0.2	3	0.2
DTPW-HB/HIB	608	99.7	608	99.3	1216	99.5	602	99.5	1818	99.5
OPV	609	99.8	608	99.3	1217	99.6	602	99.5	1819	99.6
Dose 2										
	HRV_2D N = 579		HRV_3D N = 568		HRV_POOL N = 1147		Placebo N = 576		Total N = 1723	
	n	%	n	%	n	%	n	%	n	%
Any	576	99.5	563	99.1	1139	99.3	574	99.7	1713	99.4
DTP+HIB	0	0.0	1	0.2	1	0.1	0	0.0	1	0.1
DTPW-HB/HIB	576	99.5	561	98.8	1137	99.1	574	99.7	1711	99.3
HBV	0	0.0	1	0.2	1	0.1	0	0.0	1	0.1
OPV	576	99.5	563	99.1	1139	99.3	574	99.7	1713	99.4
Dose 3										
	HRV_2D N = 560		HRV_3D N = 554		HRV_POOL N = 1114		Placebo N = 560		Total N = 1674	
	n	%	n	%	n	%	n	%	n	%
Any	555	99.1	548	98.9	1103	99.0	559	99.8	1662	99.3
DTPW-HB/HIB	555	99.1	548	98.9	1103	99.0	559	99.8	1662	99.3
OPV	555	99.1	548	98.9	1103	99.0	559	99.8	1662	99.3

N = number of subject having received considered study vaccine dose
n (%)=number (percentage) of subject having received the specified vaccination on the same day with considered study

Supplement 27 Summary of co-administered vaccination by dose - South Africa Cohort 2 (Total vaccinated cohort)

Dose 1										
Category	HRV_2D N = 447		HRV_3D N = 447		HRV_POOL N = 894		Placebo N = 445		Total N = 1339	
	n	%	n	%	n	%	n	%	n	%
Any	445	99.6	446	99.8	891	99.7	445	100	1336	99.8
BCG	0	0.0	2	0.4	2	0.2	1	0.2	3	0.2
DTPW-HB	445	99.6	446	99.8	891	99.7	445	100	1336	99.8
HIB	445	99.6	446	99.8	891	99.7	445	100	1336	99.8
OPV	445	99.6	446	99.8	891	99.7	445	100	1336	99.8
Dose 2										
	HRV_2D N = 428		HRV_3D N = 434		HRV_POOL N = 862		Placebo N = 429		Total N = 1291	
	n	%	n	%	n	%	n	%	n	%
Any	424	99.1	430	99.1	854	99.1	425	99.1	1279	99.1
BCG	1	0.2	0	0.0	1	0.1	0	0.0	1	0.1
DTPW-HB	424	99.1	430	99.1	854	99.1	425	99.1	1279	99.1
HIB	424	99.1	430	99.1	854	99.1	425	99.1	1279	99.1
OPV	424	99.1	430	99.1	854	99.1	425	99.1	1279	99.1
Dose 3										
	HRV_2D N = 422		HRV_3D N = 426		HRV_POOL N = 848		Placebo N = 423		Total N = 1271	
	n	%	n	%	n	%	n	%	n	%
Any	420	99.5	425	99.8	845	99.6	422	99.8	1267	99.7
DTPW-HB	420	99.5	425	99.8	845	99.6	422	99.8	1267	99.7
HIB	420	99.5	425	99.8	845	99.6	422	99.8	1267	99.7
OPV	420	99.5	425	99.8	845	99.6	422	99.8	1267	99.7

N = number of subject having received considered study vaccine dose
n (%)=number (percentage) of subject having received the specified vaccination on the same day with considered study dose.

Supplement 28 Summary of co-administered vaccination by dose - South Africa (Total vaccinated cohort)

Dose 1										
Category	HRV_2D N = 1057		HRV_3D N = 1059		HRV_POOL N = 2116		Placebo N = 1050		Total N = 3166	
	n	%	n	%	n	%	n	%	n	%
Any	1054	99.7	1054	99.5	2108	99.6	1047	99.7	3155	99.7
BCG	1	0.1	3	0.3	4	0.2	2	0.2	6	0.2
DTPW-HB	445	42.1	446	42.1	891	42.1	445	42.4	1336	42.2
DTPW-HB/HIB	608	57.5	608	57.4	1216	57.5	602	57.3	1818	57.4
HIB	445	42.1	446	42.1	891	42.1	445	42.4	1336	42.2
OPV	1054	99.7	1054	99.5	2108	99.6	1047	99.7	3155	99.7
Dose 2										
	HRV_2D N = 1007		HRV_3D N = 1002		HRV_POOL N = 2009		Placebo N = 1005		Total N = 3014	
	n	%	n	%	n	%	n	%	n	%
Any	1000	99.3	993	99.1	1993	99.2	999	99.4	2992	99.3
BCG	1	0.1	0	0.0	1	0.0	0	0.0	1	0.0
DTP+HIB	0	0.0	1	0.1	1	0.0	0	0.0	1	0.0
DTPW-HB	424	42.1	430	42.9	854	42.5	425	42.3	1279	42.4
DTPW-HB/HIB	576	57.2	561	56.0	1137	56.6	574	57.1	1711	56.8
HBV	0	0.0	1	0.1	1	0.0	0	0.0	1	0.0
HIB	424	42.1	430	42.9	854	42.5	425	42.3	1279	42.4
OPV	1000	99.3	993	99.1	1993	99.2	999	99.4	2992	99.3
Dose 3										
	HRV_2D N = 982		HRV_3D N = 980		HRV_POOL N = 1962		Placebo N = 983		Total N = 2945	
	n	%	n	%	n	%	n	%	n	%
Any	975	99.3	973	99.3	1948	99.3	981	99.8	2929	99.5
DTPW-HB	420	42.8	425	43.4	845	43.1	422	42.9	1267	43.0
DTPW-HB/HIB	555	56.5	548	55.9	1103	56.2	559	56.9	1662	56.4
HIB	420	42.8	425	43.4	845	43.1	422	42.9	1267	43.0
OPV	975	99.3	973	99.3	1948	99.3	981	99.8	2929	99.5

N = number of subject having received considered study vaccine dose
n (%)=number (percentage) of subject having received the specified vaccination on the same day with considered study dose.

Supplement 29 Summary of co-administered vaccinations by dose 1 - Malawi (Total vaccinated cohort)

Dose 1										
Category	HRV_2D N = 590		HRV_3D N = 592		HRV_POOL N = 1182		Placebo N = 591		Total N = 1773	
	n	%	n	%	n	%	**n**	%	n	%
Any	590	100	592	100	1182	100	591	100	1773	100
BCG	41	6.9	41	6.9	82	6.9	38	6.4	120	6.8
DTPW-HB	590	100	592	100	1182	100	591	100	1773	100
HIB	589	99.8	592	100	1181	99.9	591	100	1772	99.9
OPV	588	99.7	592	100	1180	99.8	591	100	1771	99.9
Dose 2										
	HRV_2D N = 554		HRV_3D N = 531		HRV_POOL N = 1085		Placebo N = 536		Total N = 1621	
	n	%	n	%	n	%	**n**	%	n	%
Any	550	99.3	529	99.6	1079	99.4	531	99.1	1610	99.3
BCG	15	2.7	7	1.3	22	2.0	14	2.6	36	2.2
DTPW-HB	550	99.3	528	99.4	1078	99.4	530	98.9	1608	99.2
HIB	550	99.3	528	99.4	1078	99.4	531	99.1	1609	99.3
OPV	550	99.3	528	99.4	1078	99.4	531	99.1	1609	99.3
Dose 3										
	HRV_2D N = 541		HRV_3D N = 516		HRV_POOL N = 1057		Placebo N = 513		Total N = 1570	
	n	%	n	%	n	%	**n**	%	n	%
Any	535	98.9	514	99.6	1049	99.2	507	98.8	1556	99.1
BCG	7	1.3	3	0.6	10	0.9	6	1.2	16	1.0
DTPW-HB	534	98.7	514	99.6	1048	99.1	507	98.8	1555	99.0
HIB	535	98.9	514	99.6	1049	99.2	506	98.6	1555	99.0
Me	0	0.0	1	0.2	1	0.1	0	0.0	1	0.1
OPV	535	98.9	514	99.6	1049	99.2	507	98.8	1556	99.1

N = number of subject having received considered study vaccine dose
n (%)=number (percentage) of subject having received the specified vaccination on the same day with considered study dose.

Supplement 30 Summary of vaccinations other than HRV/Placebo administered from birth to Visit 6, excluding vaccination given on the day of HRV/placebo vaccine (Total vaccinated cohort)

Before Dose 1															
	HRV_2D N = 1647			HRV_3D N = 1651			HRV_POOL N = 3298			Placebo N = 1641			Total N = 4939		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	2998	1524	92.5	3017	1542	93.4	6015	3066	93.0	2987	1526	93.0	9002	4592	93.0
BCG	1521	1520	92.3	1531	1531	92.7	3052	3051	92.5	1521	1521	92.7	4573	4572	92.6
DTP+HIB	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
DTPw+HBV	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
DTPw+HBV+HIB	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
HBV	1	1	0.1	1	1	0.1	2	2	0.1	0	0	0.0	2	2	0.0
HBV+HIB	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
HIB	1	1	0.1	0	0	0.0	1	1	0.0	0	0	0.0	1	1	0.0
OPV	1475	1455	88.3	1481	1466	88.8	2956	2921	88.6	1466	1447	88.2	4422	4368	88.4
Between Dose 1 and Dose 2 §															
	HRV_2D N = 1647			HRV_3D N = 1651			HRV_POOL N = 3298			Placebo N = 1641			Total N = 4939		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	84	39	2.4	64	43	2.6	148	82	2.5	91	50	3.0	239	132	2.7
BCG	24	24	1.5	30	30	1.8	54	54	1.6	33	33	2.0	87	87	1.8
DTP	2	2	0.1	1	1	0.1	3	3	0.1	2	1	0.1	5	4	0.1
DTP+HBV+HIB	4	2	0.1	0	0	0.0	4	2	0.1	0	0	0.0	4	2	0.0
DTP+HIB	2	2	0.1	1	1	0.1	3	3	0.1	3	3	0.2	6	6	0.1
DTPW-HB	9	8	0.5	3	3	0.2	12	11	0.3	9	9	0.5	21	20	0.4
DTPW-HB/HIB	1	1	0.1	5	5	0.3	6	6	0.2	3	3	0.2	9	9	0.2
DTPw+HBV	1	1	0.1	0	0	0.0	1	1	0.0	1	1	0.1	2	2	0.0
DTPw+HIB	1	1	0.1	3	3	0.2	4	4	0.1	1	1	0.1	5	5	0.1
HBV	5	5	0.3	5	4	0.2	10	9	0.3	4	4	0.2	14	13	0.3
HBV+HIB	1	1	0.1	0	0	0.0	1	1	0.0	0	0	0.0	1	1	0.0
HIB	11	10	0.6	4	4	0.2	15	14	0.4	12	11	0.7	27	25	0.5
Me	2	2	0.1	2	2	0.1	4	4	0.1	0	0	0.0	4	4	0.1
OPV	21	17	1.0	10	10	0.6	31	27	0.8	23	22	1.3	54	49	1.0
Between Dose 2 and Dose 3 *															
	HRV_2D N = 1561			HRV_3D N = 1533			HRV_POOL N = 3094			Placebo N = 1541			Total N = 4635		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	34	16	1.0	50	20	1.3	84	36	1.2	40	15	1.0	124	51	1.1
BCG	7	7	0.4	5	5	0.3	12	12	0.4	1	1	0.1	13	13	0.3
DTP	1	1	0.1	2	2	0.1	3	3	0.1	2	2	0.1	5	5	0.1
DTP+HIB	0	0	0.0	4	4	0.3	4	4	0.1	1	1	0.1	5	5	0.1
DTPW-HB	6	5	0.3	5	5	0.3	11	10	0.3	5	5	0.3	16	15	0.3
DTPW-HB/HIB	2	2	0.1	2	2	0.1	4	4	0.1	1	1	0.1	5	5	0.1
DTPw+HBV	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.1	1	1	0.0
DTPw+HIB	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.1	1	1	0.0
HBV	1	1	0.1	6	6	0.4	7	7	0.2	2	2	0.1	9	9	0.2
HIB	6	5	0.3	6	6	0.4	12	11	0.4	7	7	0.5	19	18	0.4
Me	2	2	0.1	6	6	0.4	8	8	0.3	8	8	0.5	16	16	0.3
OPV	9	8	0.5	14	13	0.8	23	21	0.7	11	10	0.6	34	31	0.7
Between Dose 3 and Visit 6µ															
	HRV_2D N = 1523			HRV_3D N = 1496			HRV_POOL N = 3019			Placebo N = 1496			Total N = 4515		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	1849	1361	89.4	1828	1327	88.7	3677	2688	89.0	1796	1330	88.9	5473	4018	89.0

Before Dose 1															
	HRV_2D N = 1647			HRV_3D N = 1651			HRV_POOL N = 3298			Placebo N = 1641			Total N = 4939		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
BCG	4	4	0.3	5	5	0.3	9	9	0.3	4	4	0.3	13	13	0.3
DTP	1	1	0.1	0	0	0.0	1	1	0.0	0	0	0.0	1	1	0.0
DTPW-HB	0	0	0.0	1	1	0.1	1	1	0.0	2	2	0.1	3	3	0.1
DTPW-HB/HIB	3	3	0.2	2	2	0.1	5	5	0.2	0	0	0.0	5	5	0.1
HIB	1	1	0.1	2	2	0.1	3	3	0.1	2	2	0.1	5	5	0.1
Me	1342	1342	88.1	1308	1307	87.4	2650	2649	87.7	1312	1312	87.7	3962	3961	87.7
OPV	498	345	22.7	510	339	22.7	1008	684	22.7	476	319	21.3	1484	1003	22.2

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo
Between Dose 3 and Visit 6: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered

µ= up to last contact if Visit 6 was not done

Supplement 31 Summary of vaccinations other than HRV/Placebo administered from birth to Visit 6, excluding vaccination given on the day of HRV/placebo vaccine – South Africa Cohort 1 (Total vaccinated cohort)

Before Dose 1															
	HRV_2D N = 610			HRV_3D N = 612			HRV_POOL N = 1222			Placebo N = 605			Total N = 1827		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	1205	600	98.4	1222	610	99.7	2427	1210	99.0	1205	604	99.8	3632	1814	99.3
BCG	601	600	98.4	610	610	99.7	1211	1210	99.0	603	603	99.7	1814	1813	99.2
DTP+HIB	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
HBV	1	1	0.2	1	1	0.2	2	2	0.2	0	0	0.0	2	2	0.1
HIB	1	1	0.2	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.1
OPV	602	600	98.4	610	609	99.5	1212	1209	98.9	602	602	99.5	1814	1811	99.1
Between Dose 1 and Dose 2 §															
	HRV_2D N = 610			HRV_3D N = 612			HRV_POOL N = 1222			Placebo N = 605			Total N = 1827		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	10	3	0.5	21	9	1.5	31	12	1.0	21	7	1.2	52	19	1.0
DTP	0	0	0.0	0	0	0.0	0	0	0.0	2	1	0.2	2	1	0.1
DTP+HBV+HIB	2	1	0.2	0	0	0.0	2	1	0.1	0	0	0.0	2	1	0.1
DTP+HIB	0	0	0.0	1	1	0.2	1	1	0.1	2	2	0.3	3	3	0.2
DTPW-HB/HIB	1	1	0.2	5	5	0.8	6	6	0.5	3	3	0.5	9	9	0.5
DTPw+HIB	1	1	0.2	3	3	0.5	4	4	0.3	1	1	0.2	5	5	0.3
HBV	1	1	0.2	4	3	0.5	5	4	0.3	3	3	0.5	8	7	0.4
HIB	0	0	0.0	0	0	0.0	0	0	0.0	2	1	0.2	2	1	0.1
Me	1	1	0.2	2	2	0.3	3	3	0.2	0	0	0.0	3	3	0.2
OPV	4	3	0.5	6	6	1.0	10	9	0.7	8	7	1.2	18	16	0.9
Between Dose 2 and Dose 3 *															
	HRV_2D N = 579			HRV_3D N = 568			HRV_POOL N = 1147			Placebo N = 576			Total N = 1723		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	9	4	0.7	23	8	1.4	32	12	1.0	14	6	1.0	46	18	1.0
DTP	1	1	0.2	2	2	0.4	3	3	0.3	1	1	0.2	4	4	0.2
DTP+HIB	0	0	0.0	3	3	0.5	3	3	0.3	1	1	0.2	4	4	0.2
DTPW-HB/HIB	2	2	0.3	2	2	0.4	4	4	0.3	1	1	0.2	5	5	0.3
DTPw+HIB	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.2	1	1	0.1
HBV	1	1	0.2	5	5	0.9	6	6	0.5	2	2	0.3	8	8	0.5
HIB	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
Me	2	2	0.3	3	3	0.5	5	5	0.4	5	5	0.9	10	10	0.6
OPV	3	3	0.5	7	7	1.2	10	10	0.9	3	3	0.5	13	13	0.8
Between Dose 3 and Visit 6µ															
	HRV_2D N = 560			HRV_3D N = 554			HRV_POOL N = 1114			Placebo N = 560			Total N = 1674		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	510	473	84.5	490	462	83.4	1000	935	83.9	505	486	86.8	1505	1421	84.9
BCG	2	2	0.4	0	0	0.0	2	2	0.2	0	0	0.0	2	2	0.1
DTP	1	1	0.2	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.1
DTPW-HB/HIB	3	3	0.5	2	2	0.4	5	5	0.4	0	0	0.0	5	5	0.3
HIB	1	1	0.2	1	1	0.2	2	2	0.2	0	0	0.0	2	2	0.1
Me	472	472	84.3	461	460	83.0	933	932	83.7	485	485	86.6	1418	1417	84.6
OPV	31	31	5.5	26	24	4.3	57	55	4.9	20	19	3.4	77	74	4.4

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo

Between Dose 3 and Visit 6: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered
µ= up to last contact if Visit 6 was not done

Supplement 32 Summary of vaccinations other than HRV/Placebo administered from birth to Visit 6, excluding vaccination given on the day of HRV/placebo vaccine - South Africa Cohort 2 (Total vaccinated cohort)

Before Dose 1															
	HRV_2D N = 447			HRV_3D N = 447			HRV_POOL N = 894			Placebo N = 445			Total N = 1339		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	897	441	98.7	900	444	99.3	1797	885	99.0	898	442	99.3	2695	1327	99.1
BCG	441	441	98.7	442	442	98.9	883	883	98.8	441	441	99.1	1324	1324	98.9
DTPw+HBV	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
HBV+HIB	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
OPV	456	438	98.0	456	442	98.9	912	880	98.4	457	438	98.4	1369	1318	98.4
Between Dose 1 and Dose 2 §															
	HRV_2D N = 447			HRV_3D N = 447			HRV_POOL N = 894			Placebo N = 445			Total N = 1339		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	31	8	1.8	11	4	0.9	42	12	1.3	16	6	1.3	58	18	1.3
BCG	0	0	0.0	1	1	0.2	1	1	0.1	2	2	0.4	3	3	0.2
DTP	2	2	0.4	1	1	0.2	3	3	0.3	0	0	0.0	3	3	0.2
DTP+HBV+HIB	2	1	0.2	0	0	0.0	2	1	0.1	0	0	0.0	2	1	0.1
DTP+HIB	2	2	0.4	0	0	0.0	2	2	0.2	1	1	0.2	3	3	0.2
DTPW-HB	3	3	0.7	2	2	0.4	5	5	0.6	3	3	0.7	8	8	0.6
DTPw+HBV	1	1	0.2	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.1
HBV	4	4	0.9	1	1	0.2	5	5	0.6	1	1	0.2	6	6	0.4
HBV+HIB	1	1	0.2	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.1
HIB	5	5	1.1	3	3	0.7	8	8	0.9	3	3	0.7	11	11	0.8
Me	1	1	0.2	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.1
OPV	10	8	1.8	3	3	0.7	13	11	1.2	6	6	1.3	19	17	1.3
Between Dose 2 and Dose 3 *															
	HRV_2D N = 428			HRV_3D N = 434			HRV_POOL N = 862			Placebo N = 429			Total N = 1291		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	6	2	0.5	11	3	0.7	17	5	0.6	11	3	0.7	28	8	0.6
DTP	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.2	1	1	0.1
DTP+HIB	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
DTPW-HB	2	2	0.5	2	2	0.5	4	4	0.5	2	2	0.5	6	6	0.5
HBV	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
HIB	2	2	0.5	2	2	0.5	4	4	0.5	3	3	0.7	7	7	0.5
Me	0	0	0.0	1	1	0.2	1	1	0.1	1	1	0.2	2	2	0.2
OPV	2	2	0.5	4	3	0.7	6	5	0.6	4	3	0.7	10	8	0.6
Between Dose 3 and Visit 6µ															
	HRV_2D N = 422			HRV_3D N = 426			HRV_POOL N = 848			Placebo N = 423			Total N = 1271		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	852	403	95.5	863	398	93.4	1715	801	94.5	833	393	92.9	2548	1194	93.9
BCG	1	1	0.2	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.1
DTPW-HB	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.2	1	1	0.1
HIB	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.2	1	1	0.1
Me	385	385	91.2	380	380	89.2	765	765	90.2	376	376	88.9	1141	1141	89.8
OPV	466	313	74.2	483	314	73.7	949	627	73.9	455	299	70.7	1404	926	72.9

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo
Between Dose 3 and Visit 6: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered
µ= up to last contact if Visit 6 was not done

Supplement 33 Summary of vaccinations other than HRV/Placebo administered from birth to Visit 6, excluding vaccination given on the day of HRV/placebo vaccine – South Africa (Total vaccinated cohort)

Before Dose 1															
	HRV_2D N = 1057			HRV_3D N = 1059			HRV_POOL N = 2116			Placebo N = 1050			Total N = 3166		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	2102	1041	98.5	2122	1054	99.5	4224	2095	99.0	2103	1046	99.6	6327	3141	99.2
BCG	1042	1041	98.5	1052	1052	99.3	2094	2093	98.9	1044	1044	99.4	3138	3137	99.1
DTP+HIB	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
DTPw+HBV	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
HBV	1	1	0.1	1	1	0.1	2	2	0.1	0	0	0.0	2	2	0.1
HBV+HIB	0	0	0.0	1	1	0.1	1	1	0.0	0	0	0.0	1	1	0.0
HIB	1	1	0.1	0	0	0.0	1	1	0.0	0	0	0.0	1	1	0.0
OPV	1058	1038	98.2	1066	1051	99.2	2124	2089	98.7	1059	1040	99.0	3183	3129	98.8
Between Dose 1 and Dose 2 §															
	HRV_2D N = 1057			HRV_3D N = 1059			HRV_POOL N = 2116			Placebo N = 1050			Total N = 3166		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	41	11	1.0	32	13	1.2	73	24	1.1	37	13	1.2	110	37	1.2
BCG	0	0	0.0	1	1	0.1	1	1	0.0	2	2	0.2	3	3	0.1
DTP	2	2	0.2	1	1	0.1	3	3	0.1	2	1	0.1	5	4	0.1
DTP+HBV+HIB	4	2	0.2	0	0	0.0	4	2	0.1	0	0	0.0	4	2	0.1
DTP+HIB	2	2	0.2	1	1	0.1	3	3	0.1	3	3	0.3	6	6	0.2
DTPW-HB	3	3	0.3	2	2	0.2	5	5	0.2	3	3	0.3	8	8	0.3
DTPW-HB/HIB	1	1	0.1	5	5	0.5	6	6	0.3	3	3	0.3	9	9	0.3
DTPw+HBV	1	1	0.1	0	0	0.0	1	1	0.0	0	0	0.0	1	1	0.0
DTPw+HIB	1	1	0.1	3	3	0.3	4	4	0.2	1	1	0.1	5	5	0.2
HBV	5	5	0.5	5	4	0.4	10	9	0.4	4	4	0.4	14	13	0.4
HBV+HIB	1	1	0.1	0	0	0.0	1	1	0.0	0	0	0.0	1	1	0.0
HIB	5	5	0.5	3	3	0.3	8	8	0.4	5	4	0.4	13	12	0.4
Me	2	2	0.2	2	2	0.2	4	4	0.2	0	0	0.0	4	4	0.1
OPV	14	11	1.0	9	9	0.8	23	20	0.9	14	13	1.2	37	33	1.0
Between Dose 2 and Dose 3 *															
	HRV_2D N = 1007			HRV_3D N = 1002			HRV_POOL N = 2009			Placebo N = 1005			Total N = 3014		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	15	6	0.6	34	11	1.1	49	17	0.8	25	9	0.9	74	26	0.9
DTP	1	1	0.1	2	2	0.2	3	3	0.1	2	2	0.2	5	5	0.2
DTP+HIB	0	0	0.0	4	4	0.4	4	4	0.2	1	1	0.1	5	5	0.2
DTPW-HB	2	2	0.2	2	2	0.2	4	4	0.2	2	2	0.2	6	6	0.2
DTPW-HB/HIB	2	2	0.2	2	2	0.2	4	4	0.2	1	1	0.1	5	5	0.2
DTPw+HIB	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.1	1	1	0.0
HBV	1	1	0.1	6	6	0.6	7	7	0.3	2	2	0.2	9	9	0.3
HIB	2	2	0.2	3	3	0.3	5	5	0.2	3	3	0.3	8	8	0.3
Me	2	2	0.2	4	4	0.4	6	6	0.3	6	6	0.6	12	12	0.4
OPV	5	5	0.5	11	10	1.0	16	15	0.7	7	6	0.6	23	21	0.7
Between Dose 3 and Visit 6µ															
	HRV_2D N = 982			HRV_3D N = 980			HRV_POOL N = 1962			Placebo N = 983			Total N = 2945		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	1362	876	89.2	1353	860	87.8	2715	1736	88.5	1338	879	89.4	4053	2615	88.8
BCG	3	3	0.3	0	0	0.0	3	3	0.2	0	0	0.0	3	3	0.1
DTP	1	1	0.1	0	0	0.0	1	1	0.1	0	0	0.0	1	1	0.0

Before Dose 1															
	HRV_2D N = 1057			HRV_3D N = 1059			HRV_POOL N = 2116			Placebo N = 1050			Total N = 3166		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
DTPW-HB	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.1	1	1	0.0
DTPW-HB/HIB	3	3	0.3	2	2	0.2	5	5	0.3	0	0	0.0	5	5	0.2
HIB	1	1	0.1	1	1	0.1	2	2	0.1	1	1	0.1	3	3	0.1
Me	857	857	87.3	841	840	85.7	1698	1697	86.5	861	861	87.6	2559	2558	86.9
OPV	497	344	35.0	509	338	34.5	1006	682	34.8	475	318	32.3	1481	1000	34.0

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo
Between Dose 3 and Visit 6: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered

µ= up to last contact if Visit 6 was not done

Supplement 34 Summary of vaccinations other than HRV/Placebo administered from birth to Visit 6, excluding vaccination given on the day of HRV/placebo vaccine -- Malawi (Total vaccinated cohort)

Before Dose 1															
	HRV_2D N = 590			HRV_3D N = 592			HRV_POOL N = 1182			Placebo N = 591			Total N = 1773		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	896	483	81.9	895	488	82.4	1791	971	82.1	884	480	81.2	2675	1451	81.8
BCG	479	479	81.2	479	479	80.9	958	958	81.0	477	477	80.7	1435	1435	80.9
DTPw+HBV+HIB	0	0	0.0	1	1	0.2	1	1	0.1	0	0	0.0	1	1	0.1
OPV	417	417	70.7	415	415	70.1	832	832	70.4	407	407	68.9	1239	1239	69.9
Between Dose 1 and Dose 2 §															
	HRV_2D N = 590			HRV_3D N = 592			HRV_POOL N = 1182			Placebo N = 591			Total N = 1773		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	43	28	4.7	32	30	5.1	75	58	4.9	54	37	6.3	129	95	5.4
BCG	24	24	4.1	29	29	4.9	53	53	4.5	31	31	5.2	84	84	4.7
DTPW-HB	6	5	0.8	1	1	0.2	7	6	0.5	6	6	1.0	13	12	0.7
DTPw+HBV	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.2	1	1	0.1
HIB	6	5	0.8	1	1	0.2	7	6	0.5	7	7	1.2	14	13	0.7
OPV	7	6	1.0	1	1	0.2	8	7	0.6	9	9	1.5	17	16	0.9
Between Dose 2 and Dose 3 *															
	HRV_2D N = 554			HRV_3D N = 531			HRV_POOL N = 1085			Placebo N = 536			Total N = 1621		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	19	10	1.8	16	9	1.7	35	19	1.8	15	6	1.1	50	25	1.5
BCG	7	7	1.3	5	5	0.9	12	12	1.1	1	1	0.2	13	13	0.8
DTPW-HB	4	3	0.5	3	3	0.6	7	6	0.6	3	3	0.6	10	9	0.6
DTPw+HBV	0	0	0.0	0	0	0.0	0	0	0.0	1	1	0.2	1	1	0.1
HIB	4	3	0.5	3	3	0.6	7	6	0.6	4	4	0.7	11	10	0.6
Me	0	0	0.0	2	2	0.4	2	2	0.2	2	2	0.4	4	4	0.2
OPV	4	3	0.5	3	3	0.6	7	6	0.6	4	4	0.7	11	10	0.6
Between Dose 3 and Visit 6µ															
	HRV_2D N = 541			HRV_3D N = 516			HRV_POOL N = 1057			Placebo N = 513			Total N = 1570		
Characteristics	#	n	%	#	n	%	#	n	%	#	n	%	#	n	%
Any	487	485	89.6	475	467	90.5	962	952	90.1	458	451	87.9	1420	1403	89.4
BCG	1	1	0.2	5	5	1.0	6	6	0.6	4	4	0.8	10	10	0.6
DTPW-HB	0	0	0.0	1	1	0.2	1	1	0.1	1	1	0.2	2	2	0.1
HIB	0	0	0.0	1	1	0.2	1	1	0.1	1	1	0.2	2	2	0.1
Me	485	485	89.6	467	467	90.5	952	952	90.1	451	451	87.9	1403	1403	89.4
OPV	1	1	0.2	1	1	0.2	2	2	0.2	1	1	0.2	3	3	0.2

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo
Between Dose 3 and Visit 6: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered

Supplement 35 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes, and severe RVGE episodes from 2 weeks after Dose3 up to Visit 6 by cohorts of South Africa (ATP cohort for efficacy)

			HRV_2D N = 971		HRV_3D N = 973		HRV_POOL N = 1944		Placebo N = 960		Total N = 2904	
Cohorts	Episode	Number of Episode	n	%	n	%	n	%	n	%	n	%
Cohort 1	GE	0	381	68.9	390	71.2	771	70.0	355	64.3	1126	68.1
		1	126	22.8	121	22.1	247	22.4	155	28.1	402	24.3
		2	31	5.6	32	5.8	63	5.7	29	5.3	92	5.6
		3	13	2.4	3	0.5	16	1.5	5	0.9	21	1.3
		4	2	0.4	1	0.2	3	0.3	6	1.1	9	0.5
		5	0	0.0	1	0.2	1	0.1	1	0.2	2	0.1
		6	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
		Any	172	31.1	158	28.8	330	30.0	197	35.7	527	31.9
	RVGE	0	525	94.9	527	96.2	1052	95.5	479	86.8	1531	92.6
		1	28	5.1	21	3.8	49	4.5	72	13.0	121	7.3
		2	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
		Any	28	5.1	21	3.8	49	4.5	73	13.2	122	7.4
	Severe GE	0	540	97.6	527	96.2	1067	96.9	515	93.3	1582	95.7
		1	12	2.2	19	3.5	31	2.8	34	6.2	65	3.9
		2	1	0.2	2	0.4	3	0.3	3	0.5	6	0.4
		Any	13	2.4	21	3.8	34	3.1	37	6.7	71	4.3
	Severe RV GE	0	549	99.3	543	99.1	1092	99.2	529	95.8	1621	98.1
		1	4	0.7	5	0.9	9	0.8	23	4.2	32	1.9
		Any	4	0.7	5	0.9	9	0.8	23	4.2	32	1.9
Cohort 2	GE	0	294	70.3	322	75.8	616	73.1	296	72.5	912	72.9
		1	87	20.8	83	19.5	170	20.2	90	22.1	260	20.8
		2	31	7.4	15	3.5	46	5.5	21	5.1	67	5.4
		3	4	1.0	5	1.2	9	1.1	0	0.0	9	0.7
		4	2	0.5	0	0.0	2	0.2	1	0.2	3	0.2
		Any	124	29.7	103	24.2	227	26.9	112	27.5	339	27.1
	RV GE	0	398	95.2	412	96.9	810	96.1	368	90.2	1178	94.2
		1	20	4.8	13	3.1	33	3.9	40	9.8	73	5.8
		Any	20	4.8	13	3.1	33	3.9	40	9.8	73	5.8
	Severe GE	0	395	94.5	413	97.2	808	95.8	384	94.1	1192	95.3
		1	21	5.0	12	2.8	33	3.9	23	5.6	56	4.5
		2	1	0.2	0	0.0	1	0.1	1	0.2	2	0.2
		4	1	0.2	0	0.0	1	0.1	0	0.0	1	0.1
		Any	23	5.5	12	2.8	35	4.2	24	5.9	59	4.7
	Severe RV GE	0	413	98.8	424	99.8	837	99.3	399	97.8	1236	98.8
		1	5	1.2	1	0.2	6	0.7	9	2.2	15	1.2
		Any	5	1.2	1	0.2	6	0.7	9	2.2	15	1.2

N = number of subject included in each group, for considered efficacy follow-up period
n (%) = number (percentage) subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 36 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RV GE episodes from 2 weeks after Dose3 up to Visit 6 by country (ATP cohort for efficacy)

			HRV_2D N = 1496		HRV_3D N = 1478		HRV_POOL N = 2974		Placebo N = 1443		Total N = 4417	
Country	Episode	Number of Episode	n	%	n	%	n	%	n	%	n	%
Malawi	GE	0	281	53.5	288	57.0	569	55.2	234	48.4	803	53.1
		1	149	28.4	149	29.5	298	28.9	167	34.6	465	30.7
		2	70	13.3	46	9.1	116	11.3	51	10.6	167	11.0
		3	21	4.0	16	3.2	37	3.6	22	4.6	59	3.9
		4	4	0.8	4	0.8	8	0.8	6	1.2	14	0.9
		5	0	0.0	2	0.4	2	0.2	3	0.6	5	0.3
		Any	244	46.5	217	43.0	461	44.8	249	51.6	710	46.9
	RV GE	0	480	91.4	465	92.1	945	91.7	422	87.4	1367	90.4
		1	45	8.6	40	7.9	85	8.3	60	12.4	145	9.6
		2	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
		Any	45	8.6	40	7.9	85	8.3	61	12.6	146	9.6
	Severe GE	0	427	81.3	416	82.4	843	81.8	366	75.8	1209	79.9
		1	79	15.0	78	15.4	157	15.2	95	19.7	252	16.7
		2	16	3.0	10	2.0	26	2.5	18	3.7	44	2.9
		3	3	0.6	1	0.2	4	0.4	2	0.4	6	0.4
		4	0	0.0	0	0.0	0	0.0	2	0.4	2	0.1
		Any	98	18.7	89	17.6	187	18.2	117	24.2	304	20.1
	Severe RV GE	0	504	96.0	485	96.0	989	96.0	445	92.1	1434	94.8
		1	21	4.0	20	4.0	41	4.0	38	7.9	79	5.2
		Any	21	4.0	20	4.0	41	4.0	38	7.9	79	5.2
South Africa	GE	0	675	69.5	712	73.2	1387	71.3	651	67.8	2038	70.2
		1	213	21.9	204	21.0	417	21.5	245	25.5	662	22.8
		2	62	6.4	47	4.8	109	5.6	50	5.2	159	5.5
		3	17	1.8	8	0.8	25	1.3	5	0.5	30	1.0
		4	4	0.4	1	0.1	5	0.3	7	0.7	12	0.4
		5	0	0.0	1	0.1	1	0.1	1	0.1	2	0.1
		6	0	0.0	0	0.0	0	0.0	1	0.1	1	0.0
		Any	296	30.5	261	26.8	557	28.7	309	32.2	866	29.8
	RV GE	0	923	95.1	939	96.5	1862	95.8	847	88.2	2709	93.3
		1	48	4.9	34	3.5	82	4.2	112	11.7	194	6.7
		2	0	0.0	0	0.0	0	0.0	1	0.1	1	0.0
		Any	48	4.9	34	3.5	82	4.2	113	11.8	195	6.7
	Severe GE	0	935	96.3	940	96.6	1875	96.5	899	93.6	2774	95.5
		1	33	3.4	31	3.2	64	3.3	57	5.9	121	4.2
		2	2	0.2	2	0.2	4	0.2	4	0.4	8	0.3
		4	1	0.1	0	0.0	1	0.1	0	0.0	1	0.0
		Any	36	3.7	33	3.4	69	3.5	61	6.4	130	4.5
	Severe RV GE	0	962	99.1	967	99.4	1929	99.2	928	96.7	2857	98.4
		1	9	0.9	6	0.6	15	0.8	32	3.3	47	1.6
		Any	9	0.9	6	0.6	15	0.8	32	3.3	47	1.6

N = number of subject included in each group, for considered efficacy follow-up period
n (%) = number (percentage) subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 37 Percentage of HIV positive subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RVGE episodes from 2 weeks after Dose 3 up to Visit 6 (ATP cohort for efficacy)

		HRV_2D N = 22		HRV_3D N = 31		HRV_POOL N = 53		Placebo N = 20		Total N = 73	
Characteristics	Number of Episode	n	%	n	%	n	%	n	%	n	%
GE	0	9	40.9	17	54.8	26	49.1	12	60.0	38	52.1
	1	4	18.2	12	38.7	16	30.2	5	25.0	21	28.8
	2	6	27.3	1	3.2	7	13.2	2	10.0	9	12.3
	3	3	13.6	1	3.2	4	7.5	1	5.0	5	6.8
	Any	13	59.1	14	45.2	27	50.9	8	40.0	35	47.9
RVGE	0	17	77.3	30	96.8	47	88.7	18	90.0	65	89.0
	1	5	22.7	1	3.2	6	11.3	2	10.0	8	11.0
	Any	5	22.7	1	3.2	6	11.3	2	10.0	8	11.0
Severe GE	0	17	77.3	25	80.6	42	79.2	17	85.0	59	80.8
	1	4	18.2	6	19.4	10	18.9	2	10.0	12	16.4
	2	1	4.5	0	0.0	1	1.9	1	5.0	2	2.7
	Any	5	22.7	6	19.4	11	20.8	3	15.0	14	19.2
Severe RVGE	0	19	86.4	31	100	50	94.3	19	95.0	69	94.5
	1	3	13.6	0	0.0	3	5.7	1	5.0	4	5.5
	Any	3	13.6	0	0.0	3	5.7	1	5.0	4	5.5

N = number of HIV positive subjects included in each group, for considered efficacy follow-up period
n (%) = number (percentage) HIV positive subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 38 Percentage of GE episodes with no available stool results from 2 weeks after dose 3 of HRV vaccine or placebo up to Visit 6 (ATP cohort for efficacy)

Category	HRV_2D N=772		HRV_3D N=646		HRV_POOL N=1418		Placebo N=773	
LABEL	n	%	n	%	n	%	n	%
No stool results available	106	13.7	78	12.1	184	13.0	108	14.0
No stools collected	94	12.2	71	11.0	165	11.6	97	12.5
Stools collected but no results available	12	1.6	7	1.1	19	1.4	11	1.4

N = number of gastroenteritis episodes reported
n (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 39 Percentages of GE episodes with missing information for the number of looser than normal stools per day reported from 2 weeks after Dose 3 up to study end (ATP cohort for efficacy)

	HRV_2D N = 772		HRV_3D N = 646		HRV_POOL N = 1418		Placebo N = 773		Total N = 2191	
Maximum number of stool	n	%	n	%	n	%	n	%	n	%
Missing or <3	39	5.1	25	3.9	64	4.5	26	3.4	90	4.1

N = number of GE episodes reported
n (%) = number (percentage) of GE episodes reported with maximum number of looser than normal stool <3 or missing per day during the episodes

Supplement 40 Number of GE and RV GE episodes reported from 2 weeks after Dose 3 up to study end by severity using the 20-point Vesikari scale (ATP cohort for efficacy, HIV positive population)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%	n	%	n	%
GE	Mild (1-6)	11	44.0	5	29.4	16	38.1	2	16.7
	Moderate (7-10)	7	28.0	6	35.3	13	31.0	6	50.0
	Severe (>10)	6	24.0	6	35.3	12	28.6	4	33.3
	Unknown	1	4.0	0	0.0	1	2.4	0	0.0
	Any	24	96.0	17	100	41	97.6	12	100
RV GE	Moderate (7-10)	2	40.0	1	100	3	50.0	1	50.0
	Severe (>10)	3	60.0	0	0.0	3	50.0	1	50.0
	Any	5	100	1	100	6	100	2	100

n (%) = number (percentage) of specified event reported in each group by severity using the 20-point Vesikari scale among all specified event reported the considered efficacy period
Any= Any specified symptom reported and scored >0 in Vesikari severity scale
Unknown= symptom reported with Vesikari score =0

Supplement 41 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to study end by severity using the 24-point Clark scale (ATP cohort for efficacy)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 24 point Clark scale	n	%	n	%	n	%	n	%
RV	Mild (1-8)	541	70.1	428	66.3	969	68.3	481	62.2
	Moderate (9-16)	164	21.2	168	26.0	332	23.4	235	30.4
	Severe (>16)	33	4.3	26	4.0	59	4.2	35	4.5
	Unknown	34	4.4	24	3.7	58	4.1	22	2.8
	Any	738	95.6	622	96.3	1360	95.9	751	97.2
RV GE	Mild (1-8)	60	64.5	37	50.0	97	58.1	93	52.8
	Moderate (9-16)	27	29.0	31	41.9	58	34.7	69	39.2
	Severe (>16)	6	6.5	5	6.8	11	6.6	11	6.3
	Unknown	0	0.0	1	1.4	1	0.6	3	1.7
	Any	93	100	73	98.6	166	99.4	173	98.3

n (%) = number (percentage) of specified event reported in each group by severity using the 24-point Clark scale among all specified event reported the considered efficacy period
Any= Any specified symptom reported and scored >0 in Clark severity scale
Unknown= symptom reported with Clark score =0

Supplement 42 Percentage of subjects with RV GE episodes from 2 weeks after Dose 3 up to Visit 6 by G serotype and P genotype (ATP cohort for efficacy)

	HRV_2D N = 1496		HRV_3D N = 1478		HRV_POOL N = 2974		Placebo N = 1443	
Serotype	n	%	n	%	n	%	n	%
Any	93	6.2	74	5.0	167	5.6	174	12.1
G1 wild type	31	2.1	22	1.5	53	1.8	78	5.4
G2	14	0.9	17	1.2	31	1.0	24	1.7
G3	7	0.5	1	0.1	8	0.3	11	0.8
G8	15	1.0	13	0.9	28	0.9	23	1.6
G9	11	0.7	9	0.6	20	0.7	15	1.0
GX	20	1.3	14	0.9	34	1.1	31	2.1
P4	27	1.8	28	1.9	55	1.8	44	3.0
P6	20	1.3	13	0.9	33	1.1	30	2.1
P8 wild type	49	3.3	33	2.2	82	2.8	102	7.1

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 43 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6 by G serotype and P genotype (ATP cohort for efficacy)

	HRV_2D N = 1496		HRV_3D N = 1478		HRV_POOL N = 2974		Placebo N = 1443	
Serotype	n	%	n	%	n	%	n	%
Any	30	2.0	26	1.8	56	1.9	70	4.9
G1 wild type	8	0.5	9	0.6	17	0.6	23	1.6
G2	1	0.1	2	0.1	3	0.1	7	0.5
G3	2	0.1	0	0.0	2	0.1	6	0.4
G8	6	0.4	5	0.3	11	0.4	15	1.0
G9	6	0.4	2	0.1	8	0.3	9	0.6
GX	7	0.5	8	0.5	15	0.5	15	1.0
P4	5	0.3	7	0.5	12	0.4	20	1.4
P6	6	0.4	6	0.4	12	0.4	13	0.9
P8 wild type	19	1.3	13	0.9	32	1.1	38	2.6

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one severe RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 44 Percentage of subjects who were fully vaccinated (at least 2 weeks after dose3) before beginning of RV season in South Africa (ATP cohort for efficacy)

		HRV_2D N = 971		HRV_3D N = 973		HRV_POOL N = 1944		Placebo N = 960		Total N = 2904	
Characteristics	Vaccinated before RV season?	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
South Africa cohort 1	No	258	46.7	267	48.7	525	47.7	257	46.6	782	47.3
	Yes	295	53.3	281	51.3	576	52.3	295	53.4	871	52.7
South Africa cohort 2	No	235	56.2	238	56.0	473	56.1	235	57.6	708	56.6
	Yes	183	43.8	187	44.0	370	43.9	173	42.4	543	43.4
South Africa	No	493	50.8	505	51.9	998	51.3	492	51.3	1490	51.3
	Yes	478	49.2	468	48.1	946	48.7	468	48.8	1414	48.7

N = number of subjects included in each group
n (%) = number (percentage) of subjects in specified category
Starting date of RV season in South Africa is 1st of March

Supplement 45 Number of RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy)

Serotype	HRV_2D N'=93		HRV_3D N'=74		HRV_POOL N'=167		Placebo N'=176	
	n	%	n	%	n	%	n	%
G1WT+G2+G3+P4+P8WT	1	1.08	0	0.00	1	0.60	0	0.00
G1WT+G2+P4	1	1.08	1	1.35	2	1.20	0	0.00
G1WT+G2+P4+P8WT	2	2.15	1	1.35	3	1.80	1	0.57
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	2	1.14
G1WT+P4	0	0.00	0	0.00	0	0.00	1	0.57
G1WT+P6	0	0.00	0	0.00	0	0.00	2	1.14
G1WT+P8WT	27	29.03	20	27.03	47	28.14	73	41.48
G2+G8+P4	0	0.00	1	1.35	1	0.60	1	0.57
G2+P4	10	10.75	13	17.57	23	13.77	22	12.50
G2+P4+P8WT	0	0.00	1	1.35	1	0.60	0	0.00
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	1.70
G3+P8WT	6	6.45	1	1.35	7	4.19	6	3.41
G8+P4	13	13.98	11	14.86	24	14.37	19	10.80
G8+P6	1	1.08	0	0.00	1	0.60	0	0.00
G8+P8WT	1	1.08	1	1.35	2	1.20	0	0.00
G9+P6	1	1.08	1	1.35	2	1.20	0	0.00
G9+P8WT	10	10.75	8	10.81	18	10.78	15	8.52
GX	0	0.00	1	1.35	1	0.60	0	0.00
GX+P6	18	19.35	12	16.22	30	17.96	28	15.91
GX+P8WT	2	2.15	1	1.35	3	1.80	3	1.70
Unknown	0	0.00	1	1.35	1	0.60	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after dose 3 of HRV vaccine or placebo up to VISIT 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 46 Number of RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy, South Africa cohort 1)

Serotype	HRV_2D N'=28		HRV_3D N'=21		HRV_POOL N'=49		Placebo N'=74	
	n	%	n	%	n	%	n	%
G1WT+G2+G3+P4+P8WT	1	3.57	0	0.00	1	2.04	0	0.00
G1WT+G2+P4	0	0.00	1	4.76	1	2.04	0	0.00
G1WT+G2+P4+P8WT	1	3.57	1	4.76	2	4.08	0	0.00
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	2	2.70
G1WT+P6	0	0.00	0	0.00	0	0.00	1	1.35
G1WT+P8WT	15	53.57	12	57.14	27	55.10	50	67.57
G2+G8+P4	0	0.00	0	0.00	0	0.00	1	1.35
G2+P4	1	3.57	1	4.76	2	4.08	0	0.00
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	4.05
G3+P8WT	6	21.43	1	4.76	7	14.29	6	8.11
G8+P4	0	0.00	2	9.52	2	4.08	4	5.41
G9+P6	1	3.57	1	4.76	2	4.08	0	0.00
GX+P6	3	10.71	2	9.52	5	10.20	7	9.46

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 47 Number of RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy, South Africa cohort 2)

Serotype	HRV_2D N'=20		HRV_3D N'=13		HRV_POOL N'=33		Placebo N'=40	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	5.00	0	0.00	1	3.03	0	0.00
G1WT+G2+P4+P8WT	1	5.00	0	0.00	1	3.03	1	2.50
G1WT+P4	0	0.00	0	0.00	0	0.00	1	2.50
G1WT+P8WT	10	50.00	3	23.08	13	39.39	15	37.50
G2+P4	7	35.00	9	69.23	16	48.48	19	47.50
GX+P6	1	5.00	1	7.69	2	6.06	4	10.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 48 Number of RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy, South Africa)

Serotype	HRV_2D N'=48		HRV_3D N'=34		HRV_POOL N'=82		Placebo N'=114	
	n	%	n	%	n	%	n	%
G1WT+G2+G3+P4+P8WT	1	2.08	0	0.00	1	1.22	0	0.00
G1WT+G2+P4	1	2.08	1	2.94	2	2.44	0	0.00
G1WT+G2+P4+P8WT	2	4.17	1	2.94	3	3.66	1	0.88
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	2	1.75
G1WT+P4	0	0.00	0	0.00	0	0.00	1	0.88
G1WT+P6	0	0.00	0	0.00	0	0.00	1	0.88
G1WT+P8WT	25	52.08	15	44.12	40	48.78	65	57.02
G2+G8+P4	0	0.00	0	0.00	0	0.00	1	0.88
G2+P4	8	16.67	10	29.41	18	21.95	19	16.67
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	2.63
G3+P8WT	6	12.50	1	2.94	7	8.54	6	5.26
G8+P4	0	0.00	2	5.88	2	2.44	4	3.51
G9+P6	1	2.08	1	2.94	2	2.44	0	0.00
GX+P6	4	8.33	3	8.82	7	8.54	11	9.65

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 49 Number of RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy, Malawi)

Serotype	HRV_2D N'=45		HRV_3D N'=40		HRV_POOL N'=85		Placebo N'=62	
	n	%	n	%	n	%	n	%
G1WT+P6	0	0.00	0	0.00	0	0.00	1	1.61
G1WT+P8WT	2	4.44	5	12.50	7	8.24	8	12.90
G2+G8+P4	0	0.00	1	2.50	1	1.18	0	0.00
G2+P4	2	4.44	3	7.50	5	5.88	3	4.84
G2+P4+P8WT	0	0.00	1	2.50	1	1.18	0	0.00
G8+P4	13	28.89	9	22.50	22	25.88	15	24.19
G8+P6	1	2.22	0	0.00	1	1.18	0	0.00
G8+P8WT	1	2.22	1	2.50	2	2.35	0	0.00
G9+P8WT	10	22.22	8	20.00	18	21.18	15	24.19
GX	0	0.00	1	2.50	1	1.18	0	0.00
GX+P6	14	31.11	9	22.50	23	27.06	17	27.42
GX+P8WT	2	4.44	1	2.50	3	3.53	3	4.84
Unknown	0	0.00	1	2.50	1	1.18	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 50 Number of severe RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6, by G and P type (ATP cohort for efficacy, South Africa cohort 1)

Serotype	HRV_2D N'=4		HRV_3D N'=5		HRV_POOL N'=9		Placebo N'=23	
	n	%	n	%	n	%	n	%
Any	4	100.0	5	100.0	9	100.0	23	100.0
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	1	4.35
G1WT+P8WT	2	50.00	4	80.00	6	66.67	13	56.52
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	13.04
G3+P8WT	2	50.00	0	0.00	2	22.22	2	8.70
G8+P4	0	0.00	0	0.00	0	0.00	2	8.70
GX+P6	0	0.00	1	20.00	1	11.11	2	8.70

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 51 Number of severe RV GE episodes reported from 2 weeks after dose 3 of HRV vaccine or placebo up to VISIT 6, by G and P type (ATP cohort for efficacy, South Africa cohort 2)

Serotype	HRV_2D N'=5		HRV_3D N'=1		HRV_POOL N'=6		Placebo N'=9	
	n	%	n	%	n	%	n	%
G1WT+G2+P4+P8WT	0	0.00	0	0.00	0	0.00	1	11.11
G1WT+P4	0	0.00	0	0.00	0	0.00	1	11.11
G1WT+P8WT	4	80.00	1	100.0	5	83.33	2	22.22
G2+P4	1	20.00	0	0.00	1	16.67	5	55.56

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit

Supplement 52 Number of severe RV GE episodes reported from 2 weeks after dose 3 of HRV vaccine or placebo up to VISIT 6, by G and P type (ATP cohort for efficacy, South Africa)

Serotype	HRV_2D N'=9		HRV_3D N'=6		HRV_POOL N'=15		Placebo N'=32	
	n	%	n	%	n	%	n	%
G1WT+G2+P4+P8WT	0	0.00	0	0.00	0	0.00	1	3.13
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	1	3.13
G1WT+P4	0	0.00	0	0.00	0	0.00	1	3.13
G1WT+P8WT	6	66.67	5	83.33	11	73.33	15	46.88
G2+P4	1	11.11	0	0.00	1	6.67	5	15.63
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	9.38
G3+P8WT	2	22.22	0	0.00	2	13.33	2	6.25
G8+P4	0	0.00	0	0.00	0	0.00	2	6.25
GX+P6	0	0.00	1	16.67	1	6.67	2	6.25

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 53 Number of severe RV GE episodes reported from 2 weeks after dose 3 of HRV vaccine or placebo up to VISIT 6, by G and P type (ATP cohort for efficacy, Malawi)

Serotype	HRV_2D N'=21		HRV_3D N'=20		HRV_POOL N'=41		Placebo N'=38	
	n	%	n	%	n	%	n	%
G1WT+P6	0	0.00	0	0.00	0	0.00	1	2.63
G1WT+P8WT	2	9.52	4	20.00	6	14.63	4	10.53
G2+P4	0	0.00	1	5.00	1	2.44	1	2.63
G2+P4+P8WT	0	0.00	1	5.00	1	2.44	0	0.00
G8+P4	4	19.05	5	25.00	9	21.95	10	26.32
G8+P6	1	4.76	0	0.00	1	2.44	0	0.00
G8+P8WT	1	4.76	0	0.00	1	2.44	0	0.00
G9+P8WT	6	28.57	2	10.00	8	19.51	9	23.68
GX	0	0.00	1	5.00	1	2.44	0	0.00
GX+P6	5	23.81	5	25.00	10	24.39	10	26.32
GX+P8WT	2	9.52	1	5.00	3	7.32	3	7.89

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from 2 weeks after Dose 3 of HRV vaccine or placebo up to Visit 6
Samples collected in case of gastroenteritis episodes from the first dose and the last visit
GX = G12 serotype

Supplement 54 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 (ATP cohort for efficacy)

		HRV_2D N = 93		HRV_3D N = 74		HRV_POOL N = 167		Placebo N = 176	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	9.1	-	9.1	-	9.1	-	9.6	-
	SD	3.8	-	3.7	-	3.8	-	3.6	-
	Median	9.0	-	9.0	-	9.0	-	10.0	-
	Minimum	2.0	-	1.0	-	1.0	-	0.0	-
	Maximum	19.0	-	19.0	-	19.0	-	19.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	1	1.4	1	0.6	4	2.3
	1 to 4 days	65	69.9	57	77.0	122	73.1	125	71.0
	5	5	5.4	9	12.2	14	8.4	19	10.8
	more than 5 days	23	24.7	7	9.5	30	18.0	28	15.9
Maximum number of looser Than normal stools/day	0	0	0.0	1	1.4	1	0.6	4	2.3
	1 to 3	12	12.9	13	17.6	25	15.0	20	11.4
	4 to 5	39	41.9	25	33.8	64	38.3	80	45.5
	more than 5	42	45.2	35	47.3	77	46.1	72	40.9
Duration of vomiting (days)	0 day	29	31.2	19	25.7	48	28.7	36	20.5
	1 day	26	28.0	18	24.3	44	26.3	49	27.8
	2 days	16	17.2	19	25.7	35	21.0	34	19.3
	more than 2 days	22	23.7	18	24.3	40	24.0	57	32.4
Max number of episodes of vomiting /day	0	29	31.2	19	25.7	48	28.7	36	20.5
	1	8	8.6	4	5.4	12	7.2	12	6.8
	2 to 4	35	37.6	30	40.5	65	38.9	80	45.5
	more than 4	21	22.6	21	28.4	42	25.1	48	27.3
Maximum fever reported/day	less than 37.1°C	20	21.5	17	23.0	37	22.2	36	20.5
	37.1 to 38.4°C	61	65.6	41	55.4	102	61.1	103	58.5
	38.5 to 38.9°C	6	6.5	9	12.2	15	9.0	21	11.9
	more than 38.9°C	6	6.5	7	9.5	13	7.8	16	9.1
Treatment	none	15	16.1	10	13.5	25	15.0	20	11.4
	rehydration	68	73.1	60	81.1	128	76.6	140	79.5
	hospitalization	10	10.8	4	5.4	14	8.4	16	9.1
Dehydration	none	73	78.5	61	82.4	134	80.2	139	79.0
	1 to 5%	16	17.2	11	14.9	27	16.2	30	17.0
	more than 5 %	4	4.3	2	2.7	6	3.6	7	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

Supplement 55 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 by G1 WT serotype (ATP cohort for efficacy)

		HRV_2D N = 31		HRV_3D N = 22		HRV_POOL N = 53		Placebo N = 79	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	7.8	-	8.7	-	8.2	-	9.1	-
	SD	2.9	-	4.3	-	3.5	-	3.4	-
	Median	7.0	-	9.0	-	8.0	-	9.0	-
	Minimum	2.0	-	1.0	-	1.0	-	0.0	-
	Maximum	14.0	-	17.0	-	17.0	-	19.0	-
Duration of looser than normal	0 day	0	0.0	1	4.5	1	1.9	2	2.5
	1 to 4 days	22	71.0	18	81.8	40	75.5	60	75.9
	5	2	6.5	1	4.5	3	5.7	7	8.9
	more than 5 days	7	22.6	2	9.1	9	17.0	10	12.7
Maximum number of looser	0	0	0.0	1	4.5	1	1.9	2	2.5
	1 to 3	7	22.6	3	13.6	10	18.9	11	13.9
	4 to 5	18	58.1	6	27.3	24	45.3	39	49.4
	more than 5	6	19.4	12	54.5	18	34.0	27	34.2
Duration of vomiting-days	0 day	11	35.5	9	40.9	20	37.7	17	21.5
	1 day	12	38.7	5	22.7	17	32.1	25	31.6
	2 days	4	12.9	4	18.2	8	15.1	21	26.6
	more than 2 days	4	12.9	4	18.2	8	15.1	16	20.3
Max number of episodes of vomiting /day	0	11	35.5	9	40.9	20	37.7	17	21.5
	1	3	9.7	0	0.0	3	5.7	4	5.1
	2 to 4	15	48.4	6	27.3	21	39.6	41	51.9
	more than 4	2	6.5	7	31.8	9	17.0	17	21.5
Maximum fever reported/day	less than 37.1°C	7	22.6	5	22.7	12	22.6	19	24.1
	37.1 to 38.4°C	20	64.5	11	50.0	31	58.5	44	55.7
	38.5 to 38.9°C	1	3.2	3	13.6	4	7.5	8	10.1
	more than 38.9°C	3	9.7	3	13.6	6	11.3	8	10.1
Treatment	none	8	25.8	4	18.2	12	22.6	12	15.2
	rehydration	22	71.0	17	77.3	39	73.6	61	77.2
	hospitalization	1	3.2	1	4.5	2	3.8	6	7.6
Dehydration	none	27	87.1	17	77.3	44	83.0	63	79.7
	1 to 5%	4	12.9	4	18.2	8	15.1	12	15.2
	more than 5 %	0	0.0	1	4.5	1	1.9	4	5.1

N = number of RV GE (G1 WT serotype) 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 56 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 by G2 serotype (ATP cohort for efficacy)

		HRV_2D N = 14		HRV_3D N = 17		HRV_POOL N = 31		Placebo N = 24	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	7.4	-	7.5	-	7.4	-	9.7	-
	SD	3.3	-	2.6	-	2.9	-	3.6	-
	Median	7.0	-	8.0	-	8.0	-	10.0	-
	Minimum	3.0	-	2.0	-	2.0	-	3.0	-
	Maximum	16.0	-	11.0	-	16.0	-	18.0	-
Duration of looser than normal	0 day	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 4 days	9	64.3	15	88.2	24	77.4	18	75.0
	5	2	14.3	1	5.9	3	9.7	1	4.2
	more than 5 days	3	21.4	1	5.9	4	12.9	5	20.8
Maximum number of looser	0	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 3	2	14.3	3	17.6	5	16.1	2	8.3
	4 to 5	10	71.4	8	47.1	18	58.1	12	50.0
	more than 5	2	14.3	6	35.3	8	25.8	10	41.7
Duration of vomiting-days	0 day	6	42.9	8	47.1	14	45.2	5	20.8
	1 day	4	28.6	4	23.5	8	25.8	9	37.5
	2 days	3	21.4	4	23.5	7	22.6	4	16.7
	more than 2 days	1	7.1	1	5.9	2	6.5	6	25.0
Max number of episodes of vomiting/day	0	6	42.9	8	47.1	14	45.2	5	20.8
	1	3	21.4	0	0.0	3	9.7	1	4.2
	2 to 4	4	28.6	5	29.4	9	29.0	14	58.3
	more than 4	1	7.1	4	23.5	5	16.1	4	16.7
Maximum fever reported/day	less than 37.1°C	4	28.6	2	11.8	6	19.4	4	16.7
	37.1 to 38.4°C	9	64.3	12	70.6	21	67.7	16	66.7
	38.5 to 38.9°C	1	7.1	2	11.8	3	9.7	3	12.5
	more than 38.9°C	0	0.0	1	5.9	1	3.2	1	4.2
Treatment	none	5	35.7	3	17.6	8	25.8	3	12.5
	rehydration	8	57.1	14	82.4	22	71.0	18	75.0
	hospitalization	1	7.1	0	0.0	1	3.2	3	12.5
Dehydration	none	12	85.7	17	100	29	93.5	17	70.8
	1 to 5%	1	7.1	0	0.0	1	3.2	5	20.8
	more than 5 %	1	7.1	0	0.0	1	3.2	2	8.3

N = number of RV GE episodes (G2 serotype) 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 57 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 by G8 serotype (ATP cohort for efficacy)

		HRV_2D N = 15		HRV_3D N = 13		HRV_POOL N = 28		Placebo N = 23	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	10.4	-	9.2	-	9.9	-	10.4	-
	SD	3.9	-	3.1	-	3.5	-	3.5	-
	Median	9.0	-	9.0	-	9.0	-	11.0	-
	Minimum	5.0	-	5.0	-	5.0	-	5.0	-
	Maximum	17.0	-	13.0	-	17.0	-	15.0	-
Duration of looser than normal	0 day	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 4 days	8	53.3	10	76.9	18	64.3	15	65.2
	5	1	6.7	2	15.4	3	10.7	3	13.0
	more than 5 days	6	40.0	1	7.7	7	25.0	5	21.7
Maximum number of looser	0	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 3	0	0.0	4	30.8	4	14.3	0	0.0
	4 to 5	3	20.0	2	15.4	5	17.9	9	39.1
	more than 5	12	80.0	7	53.8	19	67.9	14	60.9
Duration of vomiting-days	0 day	6	40.0	0	0.0	6	21.4	6	26.1
	1 day	3	20.0	5	38.5	8	28.6	1	4.3
	2 days	1	6.7	6	46.2	7	25.0	5	21.7
	more than 2 days	5	33.3	2	15.4	7	25.0	11	47.8
Maximum number of episodes of vomiting/day	0	6	40.0	0	0.0	6	21.4	6	26.1
	1	0	0.0	3	23.1	3	10.7	1	4.3
	2 to 4	2	13.3	8	61.5	10	35.7	7	30.4
	more than 4	7	46.7	2	15.4	9	32.1	9	39.1
Maximum fever reported/day	less than 37.1°C	1	6.7	4	30.8	5	17.9	2	8.7
	37.1 to 38.4°C	10	66.7	8	61.5	18	64.3	14	60.9
	38.5 to 38.9°C	3	20.0	1	7.7	4	14.3	6	26.1
	more than 38.9°C	1	6.7	0	0.0	1	3.6	1	4.3
Treatment	none	2	13.3	2	15.4	4	14.3	1	4.3
	rehydration	10	66.7	10	76.9	20	71.4	20	87.0
	hospitalization	3	20.0	1	7.7	4	14.3	2	8.7
Dehydration	none	12	80.0	11	84.6	23	82.1	21	91.3
	1 to 5%	3	20.0	2	15.4	5	17.9	2	8.7
	more than 5 %	0	0.0	0	0.0	0	0.0	0	0.0

N = number of RV GE (G8 serotype) 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 58 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 by G9 serotype (ATP cohort for efficacy)

		HRV_2D N = 11		HRV_3D N = 9		HRV_POOL N = 20		Placebo N = 15	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	11.0	-	9.3	-	10.3	-	10.3	-
	SD	4.8	-	1.5	-	3.7	-	3.2	-
	Median	11.0	-	9.0	-	9.5	-	11.0	-
	Minimum	4.0	-	7.0	-	4.0	-	3.0	-
	Maximum	19.0	-	12.0	-	19.0	-	15.0	-
Duration of looser than normal	0 day	0	0.0	0	0.0	0	0.0	1	6.7
	1 to 4 days	6	54.5	7	77.8	13	65.0	9	60.0
	5	0	0.0	2	22.2	2	10.0	4	26.7
	more than 5 days	5	45.5	0	0.0	5	25.0	1	6.7
Maximum number of looser	0	0	0.0	0	0.0	0	0.0	1	6.7
	1 to 3	1	9.1	1	11.1	2	10.0	2	13.3
	4 to 5	0	0.0	7	77.8	7	35.0	3	20.0
	more than 5	10	90.9	1	11.1	11	55.0	9	60.0
Duration of vomiting-days	0 day	3	27.3	1	11.1	4	20.0	3	20.0
	1 day	2	18.2	1	11.1	3	15.0	4	26.7
	2 days	1	9.1	4	44.4	5	25.0	1	6.7
	more than 2 days	5	45.5	3	33.3	8	40.0	7	46.7
Maximum number of episodes of vomiting/day	0	3	27.3	1	11.1	4	20.0	3	20.0
	1	0	0.0	0	0.0	0	0.0	1	6.7
	2 to 4	4	36.4	8	88.9	12	60.0	6	40.0
	more than 4	4	36.4	0	0.0	4	20.0	5	33.3
Maximum fever reported/day	less than 37.1°C	1	9.1	2	22.2	3	15.0	2	13.3
	37.1 to 38.4°C	8	72.7	5	55.6	13	65.0	11	73.3
	38.5 to 38.9°C	0	0.0	1	11.1	1	5.0	1	6.7
	more than 38.9°C	2	18.2	1	11.1	3	15.0	1	6.7
Treatment	none	0	0.0	0	0.0	0	0.0	0	0.0
	rehydration	10	90.9	9	100	19	95.0	14	93.3
	hospitalization	1	9.1	0	0.0	1	5.0	1	6.7
Dehydration	none	9	81.8	8	88.9	17	85.0	9	60.0
	1 to 5%	2	18.2	1	11.1	3	15.0	6	40.0
	more than 5 %	0	0.0	0	0.0	0	0.0	0	0.0

N = number of RV GE (G9 serotype) 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 59 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 by G12 serotype (ATP cohort for efficacy)

		HRV_2D N = 20		HRV_3D N = 14		HRV_POOL N = 34		Placebo N = 31	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	10.1	-	11.9	-	10.8	-	10.2	-
	SD	3.9	-	4.3	-	4.1	-	4.1	-
	Median	9.5	-	11.5	-	10.0	-	10.0	-
	Minimum	3.0	-	4.0	-	3.0	-	1.0	-
	Maximum	18.0	-	19.0	-	19.0	-	19.0	-
Duration of looser than normal	0 day	0	0.0	0	0.0	0	0.0	1	3.2
	1 to 4 days	17	85.0	8	57.1	25	73.5	20	64.5
	5	1	5.0	3	21.4	4	11.8	3	9.7
	more than 5 days	2	10.0	3	21.4	5	14.7	7	22.6
Maximum number of looser	0	0	0.0	0	0.0	0	0.0	1	3.2
	1 to 3	2	10.0	1	7.1	3	8.8	4	12.9
	4 to 5	7	35.0	3	21.4	10	29.4	14	45.2
	more than 5	11	55.0	10	71.4	21	61.8	12	38.7
Duration of vomiting-days	0 day	4	20.0	2	14.3	6	17.6	4	12.9
	1 day	5	25.0	2	14.3	7	20.6	9	29.0
	2 days	6	30.0	2	14.3	8	23.5	3	9.7
	more than 2 days	5	25.0	8	57.1	13	38.2	15	48.4
Maximum number of episodes of vomiting/day	0	4	20.0	2	14.3	6	17.6	4	12.9
	1	2	10.0	1	7.1	3	8.8	4	12.9
	2 to 4	7	35.0	4	28.6	11	32.4	10	32.3
	more than 4	7	35.0	7	50.0	14	41.2	13	41.9
Maximum fever reported/day	less than 37.1°C	7	35.0	2	14.3	9	26.5	8	25.8
	37.1 to 38.4°C	12	60.0	7	50.0	19	55.9	16	51.6
	38.5 to 38.9°C	1	5.0	2	14.3	3	8.8	3	9.7
	more than 38.9°C	0	0.0	3	21.4	3	8.8	4	12.9
Treatment	none	0	0.0	1	7.1	1	2.9	1	3.2
	rehydration	16	80.0	11	78.6	27	79.4	27	87.1
	hospitalization	4	20.0	2	14.3	6	17.6	3	9.7
Dehydration	none	11	55.0	9	64.3	20	58.8	25	80.6
	1 to 5%	6	30.0	4	28.6	10	29.4	6	19.4
	more than 5 %	3	15.0	1	7.1	4	11.8	0	0.0

N = number of RV GE (G12 serotype) 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 60 Characteristics of the GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 3 up to visit 6 (ATP cohort for efficacy)

		HRV_2D N = 772		HRV_3D N = 646		HRV_POOL N = 1418		Placebo N = 773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	7.4	-	7.6	-	7.5	-	8.3	-
	SD	4.0	-	3.9	-	3.9	-	3.9	-
	Median	7.0	-	7.0	-	7.0	-	8.0	-
	Minimum	0.0	-	0.0	-	0.0	-	0.0	-
	Maximum	20.0	-	19.0	-	20.0	-	20.0	-
Duration of looser than normal stools (days)	0 day	39	5.1	24	3.7	63	4.4	25	3.2
	1 to 4 days	521	67.5	440	68.1	961	67.8	518	67.0
	5	54	7.0	58	9.0	112	7.9	75	9.7
	more than 5 days	158	20.5	124	19.2	282	19.9	155	20.1
Maximum number of looser	0	39	5.1	24	3.7	63	4.4	25	3.2
	1 to 3	125	16.2	107	16.6	232	16.4	123	15.9
	4 to 5	318	41.2	290	44.9	608	42.9	319	41.3
	more than 5	290	37.6	225	34.8	515	36.3	306	39.6
Duration of vomiting-days	0 day	447	57.9	339	52.5	786	55.4	344	44.5
	1 day	137	17.7	126	19.5	263	18.5	162	21.0
	2 days	75	9.7	79	12.2	154	10.9	107	13.8
	more than 2 days	113	14.6	102	15.8	215	15.2	160	20.7
Max number of episodes of vomiting /day	0	447	57.9	339	52.5	786	55.4	344	44.5
	1	59	7.6	61	9.4	120	8.5	69	8.9
	2 to 4	175	22.7	172	26.6	347	24.5	239	30.9
	more than 4	91	11.8	74	11.5	165	11.6	121	15.7
Maximum fever reported/day	less than 37.1°C	246	31.9	185	28.6	431	30.4	212	27.4
	37.1 to 38.4°C	394	51.0	358	55.4	752	53.0	408	52.8
	38.5 to 38.9°C	40	5.2	35	5.4	75	5.3	72	9.3
	more than 38.9°C	92	11.9	68	10.5	160	11.3	81	10.5
Treatment	none	170	22.0	140	21.7	310	21.9	135	17.5
	rehydration	546	70.7	468	72.4			575	74.4
	hospitalization	56	7.3	38	5.9			63	8.2
Dehydration	none	637	82.5	540	83.6			617	79.8
	1 to 5%	112	14.5	94	14.6			127	16.4
	more than 5 %	23	3.0	12	1.9			29	3.8

N = number of 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 61 Characteristics of the RV GE episodes (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 (ATP cohort for efficacy)

		HRV_2D N = 93		HRV_3D N = 74		HRV_POOL N = 167		Placebo N = 176	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	8.0	-	8.5	-	8.2	-	8.8	-
	SD	4.5	-	4.9	-	4.7	-	4.5	-
	Median	8.0	-	8.0	-	8.0	-	8.0	-
	Minimum	2.0	-	0.0	-	0.0	-	0.0	-
	Maximum	22.0	-	21.0	-	22.0	-	22.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	1	1.4	1	0.6	4	2.3
	1 to 4 days	65	69.9	57	77.0	122	73.1	125	71.0
	5 to 7 days	23	24.7	15	20.3	38	22.8	41	23.3
	more than 7 days	5	5.4	1	1.4	6	3.6	6	3.4
Maximum number of looser Than normal stools/day	0 to 1	0	0.0	1	1.4	1	0.6	4	2.3
	2 to 4	40	43.0	31	41.9	71	42.5	65	36.9
	5 to 7	29	31.2	27	36.5	56	33.5	85	48.3
	more than 7	24	25.8	15	20.3	39	23.4	22	12.5
Duration of vomiting (days)	0-1 day	55	59.1	37	50.0	92	55.1	85	48.3
	2 days	16	17.2	19	25.7	35	21.0	34	19.3
	3-5 days	17	18.3	17	23.0	34	20.4	50	28.4
	more than 5 days	5	5.4	1	1.4	6	3.6	7	4.0
Max number of episodes of vomiting /day	0	29	31.2	19	25.7	48	28.7	36	20.5
	1 to 3	37	39.8	23	31.1	60	35.9	64	36.4
	4 to 6	18	19.4	21	28.4	39	23.4	60	34.1
	more than 6	9	9.7	11	14.9	20	12.0	16	9.1
Duration of fever (days)	0 day	64	68.8	41	55.4	105	62.9	102	58.0
	1-2 days	25	26.9	26	35.1	51	30.5	55	31.3
	3-4 days	2	2.2	6	8.1	8	4.8	14	8.0
	more than 4 days	2	2.2	1	1.4	3	1.8	5	2.8
Maximum fever reported/day	less than 38.0°C	64	68.8	41	55.4	105	62.9	102	58.0
	38.0 to 338.2°C	13	14.0	10	13.5	23	13.8	26	14.8
	38.3 to 38.7°C	8	8.6	14	18.9	22	13.2	28	15.9
	more than 38.7°C	8	8.6	9	12.2	17	10.2	20	11.4
Duration of behavioural symptoms	0 day	35	37.6	32	43.2	67	40.1	60	34.1
	1-2 days	40	43.0	22	29.7	62	37.1	74	42.0
	3-4 days	7	7.5	12	16.2	19	11.4	22	12.5
	more than 4 days	11	11.8	8	10.8	19	11.4	20	11.4
Behavioural symptoms	Behave as usual	35	37.6	32	43.2	67	40.1	60	34.1
	Irritable/Less playful	10	10.8	7	9.5	17	10.2	21	11.9
	Lethargic/listless	48	51.6	34	45.9	82	49.1	92	52.3
	Seizures	0	0.0	1	1.4	1	0.6	3	1.7

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 62 Characteristics of the RV GE episodes (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 by G1WT serotype (ATP cohort for efficacy)

		HRV_2D N = 31		HRV_3D N = 22		HRV_POOL N = 53		Placebo N = 79	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	6.7	-	7.2	-	6.9	-	7.7	-
	SD	2.9	-	4.5	-	3.6	-	3.9	-
	Median	7.0	-	6.0	-	6.0	-	8.0	-
	Minimum	2.0	-	0.0	-	0.0	-	0.0	-
	Maximum	16.0	-	16.0	-	16.0	-	19.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	1	4.5	1	1.9	2	2.5
	1 to 4 days	22	71.0	18	81.8	40	75.5	60	75.9
	5 to 7 days	8	25.8	3	13.6	11	20.8	16	20.3
	more than 7 days	1	3.2	0	0.0	1	1.9	1	1.3
Maximum number of looser	0 to 1	0	0.0	1	4.5	1	1.9	2	2.5
	2 to 4	22	71.0	6	27.3	28	52.8	32	40.5
	5 to 7	7	22.6	10	45.5	17	32.1	36	45.6
	more than 7	2	6.5	5	22.7	7	13.2	9	11.4
Duration of vomiting-days	0-1 day	23	74.2	14	63.6	37	69.8	42	53.2
	2 days	4	12.9	4	18.2	8	15.1	21	26.6
	3-5 days	4	12.9	3	13.6	7	13.2	14	17.7
	more than 5 days	0	0.0	1	4.5	1	1.9	2	2.5
Max number of episodes of vomiting /day	0	11	35.5	9	40.9	20	37.7	17	21.5
	1 to 3	17	54.8	4	18.2	21	39.6	32	40.5
	4 to 6	2	6.5	8	36.4	10	18.9	25	31.6
	more than 6	1	3.2	1	4.5	2	3.8	5	6.3
Duration of fever-days	0 day	20	64.5	11	50.0	31	58.5	51	64.6
	1-2 days	11	35.5	10	45.5	21	39.6	20	25.3
	3-4 days	0	0.0	1	4.5	1	1.9	6	7.6
	more than 4 days	0	0.0	0	0.0	0	0.0	2	2.5
Maximum fever reported/day	less than 38.0°C	20	64.5	11	50.0	31	58.5	51	64.6
	38.0 to 338.2°C	6	19.4	4	18.2	10	18.9	7	8.9
	38.3 to 38.7°C	2	6.5	4	18.2	6	11.3	12	15.2
	more than 38.7°C	3	9.7	3	13.6	6	11.3	9	11.4
Duration of behavioural symptoms	0 day	11	35.5	13	59.1	24	45.3	35	44.3
	1-2 days	17	54.8	8	36.4	25	47.2	30	38.0
	3-4 days	1	3.2	0	0.0	1	1.9	11	13.9
	more than 4 days	2	6.5	1	4.5	3	5.7	3	3.8
Behavioural symptoms	Behave as usual	11	35.5	13	59.1	24	45.3	35	44.3
	Irritable/Less playful	7	22.6	5	22.7	12	22.6	13	16.5
	Lethargic/listless	13	41.9	4	18.2	17	32.1	29	36.7
	Seizures	0	0.0	0	0.0	0	0.0	2	2.5

N = number of RV GE (G1WT serotype) 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 (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 by G2 serotype (ATP cohort for efficacy)

		HRV_2D N = 14		HRV_3D N = 17		HRV_POOL N = 31		Placebo N = 24	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	6.0	-	6.6	-	6.4	-	8.2	-
	SD	2.9	-	4.0	-	3.5	-	4.4	-
	Median	5.0	-	8.0	-	6.0	-	7.0	-
	Minimum	2.0	-	2.0	-	2.0	-	3.0	-
	Maximum	12.0	-	14.0	-	14.0	-	18.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 4 days	9	64.3	15	88.2	24	77.4	18	75.0
	5 to 7 days	5	35.7	2	11.8	7	22.6	5	20.8
	more than 7 days	0	0.0	0	0.0	0	0.0	1	4.2
Maximum number of looser	0 to 1	0	0.0	0	0.0	0	0.0	0	0.0
	2 to 4	9	64.3	10	58.8	19	61.3	9	37.5
	5 to 7	4	28.6	6	35.3	10	32.3	11	45.8
	more than 7	1	7.1	1	5.9	2	6.5	4	16.7
Duration of vomiting-days	0-1 day	10	71.4	12	70.6	22	71.0	14	58.3
	2 days	3	21.4	4	23.5	7	22.6	4	16.7
	3-5 days	1	7.1	1	5.9	2	6.5	5	20.8
	more than 5 days	0	0.0	0	0.0	0	0.0	1	4.2
Max number of episodes of vomiting /day	0	6	42.9	8	47.1	14	45.2	5	20.8
	1 to 3	6	42.9	3	17.6	9	29.0	9	37.5
	4 to 6	1	7.1	4	23.5	5	16.1	10	41.7
	more than 6	1	7.1	2	11.8	3	9.7	0	0.0
Duration of fever-days	0 day	11	78.6	10	58.8	21	67.7	13	54.2
	1-2 days	3	21.4	6	35.3	9	29.0	10	41.7
	3-4 days	0	0.0	1	5.9	1	3.2	1	4.2
	more than 4 days	0	0.0	0	0.0	0	0.0	0	0.0
Maximum fever reported/day	less than 38.0°C	11	78.6	10	58.8	21	67.7	13	54.2
	38.0 to 338.2°C	1	7.1	0	0.0	1	3.2	5	20.8
	38.3 to 38.7°C	1	7.1	5	29.4	6	19.4	5	20.8
	more than 38.7°C	1	7.1	2	11.8	3	9.7	1	4.2
Duration of behavioural symptoms	0 day	6	42.9	10	58.8	16	51.6	11	45.8
	1-2 days	8	57.1	5	29.4	13	41.9	8	33.3
	3-4 days	0	0.0	2	11.8	2	6.5	2	8.3
	more than 4 days	0	0.0	0	0.0	0	0.0	3	12.5
Behaviral symptoms	Behave as usual	6	42.9	10	58.8	16	51.6	11	45.8
	Irritable/Less playful	4	28.6	1	5.9	5	16.1	1	4.2
	Lethargic/listless	4	28.6	6	35.3	10	32.3	12	50.0
	Seizures	0	0.0	0	0.0	0	0.0	0	0.0

N = number of RV GE (G2 serotype) 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 (based on Clark scale) reported from 2 weeks after Dose 3 up to Visit 6 by G3 serotype (ATP cohort for efficacy)

		HRV_2D N = 7		HRV_3D N = 1		HRV_POOL N = 8		Placebo N = 11	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	5.6	-	3.0	-	5.3	-	9.0	-
	SD	3.7	-	0.0	-	3.5	-	2.9	-
	Median	4.0	-	3.0	-	3.5	-	9.0	-
	Minimum	2.0	-	3.0	-	2.0	-	2.0	-
	Maximum	11.0	-	3.0	-	11.0	-	13.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 4 days	6	85.7	1	100	7	87.5	9	81.8
	5 to 7 days	1	14.3	0	0.0	1	12.5	1	9.1
	more than 7 days	0	0.0	0	0.0	0	0.0	1	9.1
Maximum number of looser	0 to 1	0	0.0	0	0.0	0	0.0	0	0.0
	2 to 4	4	57.1	1	100	5	62.5	5	45.5
	5 to 7	1	14.3	0	0.0	1	12.5	5	45.5
	more than 7	2	28.6	0	0.0	2	25.0	1	9.1
Duration of vomiting-days	0-1 day	4	57.1	1	100	5	62.5	5	45.5
	2 days	1	14.3	0	0.0	1	12.5	2	18.2
	3-5 days	2	28.6	0	0.0	2	25.0	4	36.4
	more than 5 days	0	0.0	0	0.0	0	0.0	0	0.0
Max number o f episodes of vomiting/day	0	3	42.9	0	0.0	3	37.5	2	18.2
	1 to 3	3	42.9	1	100	4	50.0	4	36.4
	4 to 6	1	14.3	0	0.0	1	12.5	5	45.5
	more than 6	0	0.0	0	0.0	0	0.0	0	0.0
Duration of fever-days	0 day	5	71.4	1	100	6	75.0	6	54.5
	1-2 days	2	28.6	0	0.0	2	25.0	5	45.5
	3-4 days	0	0.0	0	0.0	0	0.0	0	0.0
	more than 4 days	0	0.0	0	0.0	0	0.0	0	0.0
Maximum fever reported/day	less than 38.0°C	5	71.4	1	100	6	75.0	6	54.5
	38.0 to 338.2°C	1	14.3	0	0.0	1	12.5	2	10.5
	38.3 to 38.7°C	1	14.3	0	0.0	1	12.5	3	15.8
	more than 38.7°C	0	0.0	0	0.0	0	0.0	2	10.5
Duration of behavioural symptoms	0 day	5	71.4	1	100	6	75.0	8	42.1
	1-2 days	2	28.6	0	0.0	2	25.0	10	52.6
	3-4 days	0	0.0	0	0.0	0	0.0	0	0.0
	more than 4 days	0	0.0	0	0.0	0	0.0	1	5.3
Behavioural symptoms	Behave as usual	5	71.4	1	100	6	75.0	8	42.1
	Irritable/Less playful	2	28.6	0	0.0	2	25.0	4	21.1
	Lethargic/listless	0	0.0	0	0.0	0	0.0	7	36.8
	Seizures	0	0.0	0	0.0	0	0.0	0	0.0

N = number of RV GE episodes (G3 serotype) 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 (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 by G8 serotype (ATP cohort for efficacy)

		HRV_2D N = 15		HRV_3D N = 13		HRV_POOL N = 28		Placebo N = 23	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	10.3	-	8.8	-	9.6	-	10.4	-
	SD	6.0	-	4.4	-	5.3	-	3.8	-
	Median	10.0	-	8.0	-	9.0	-	10.0	-
	Minimum	2.0	-	3.0	-	2.0	-	4.0	-
	Maximum	22.0	-	17.0	-	22.0	-	18.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0	0	0.0	0	0.0
	1 to 4 days	8	53.3	10	76.9	18	64.3	15	65.2
	5 to 7 days	3	20.0	3	23.1	6	21.4	6	26.1
	more than 7 days	4	26.7	0	0.0	4	14.3	2	8.7
Maximum number of looser	0 to 1	0	0.0	0	0.0	0	0.0	0	0.0
	2 to 4	2	13.3	5	38.5	7	25.0	5	21.7
	5 to 7	7	46.7	5	38.5	12	42.9	12	52.2
	more than 7	6	40.0	3	23.1	9	32.1	6	26.1
Duration of vomiting-days	0-1 day	9	60.0	5	38.5	14	50.0	7	30.4
	2 days	1	6.7	6	46.2	7	25.0	5	21.7
	3-5 days	2	13.3	2	15.4	4	14.3	9	39.1
	more than 5 days	3	20.0	0	0.0	3	10.7	2	8.7
Max number of episodes of vomiting /day	0	6	40.0	0	0.0	6	21.4	6	26.1
	1 to 3	1	6.7	9	69.2	10	35.7	4	17.4
	4 to 6	5	33.3	2	15.4	7	25.0	10	43.5
	more than 6	3	20.0	2	15.4	5	17.9	3	13.0
Duration of fever-days	0 day	9	60.0	8	61.5	17	60.7	11	47.8
	1-2 days	4	26.7	5	38.5	9	32.1	10	43.5
	3-4 days	1	6.7	0	0.0	1	3.6	1	4.3
	more than 4 days	1	6.7	0	0.0	1	3.6	1	4.3
Maximum fever reported/day	less than 38.0°C	9	60.0	8	61.5	17	60.7	11	47.8
	38.0 to 338.2°C	2	13.3	2	15.4	4	14.3	5	21.7
	38.3 to 38.7°C	2	13.3	3	23.1	5	17.9	6	26.1
	more than 38.7°C	2	13.3	0	0.0	2	7.1	1	4.3
Duration of behavioural symptoms	0 day	5	33.3	4	30.8	9	32.1	4	17.4
	1-2 days	5	33.3	4	30.8	9	32.1	14	60.9
	3-4 days	1	6.7	3	23.1	4	14.3	3	13.0
	more than 4 days	4	26.7	2	15.4	6	21.4	2	8.7
Behavioural symptoms	Behave as usual	5	33.3	4	30.8	9	32.1	4	17.4
	Irritable/Less playful	0	0.0	2	15.4	2	7.1	1	4.3
	Lethargic/listless	10	66.7	7	53.8	17	60.7	18	78.3
	Seizures	0	0.0	0	0.0	0	0.0	0	0.0

N = number of RV GE (G8 serotype) 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 Characteristics of the RV GE episodes (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 by G9 serotype (ATP cohort for efficacy)

		HRV_2D N = 11		HRV_3D N = 9		HRV_POOL N = 20		Placebo N = 15	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	10.5	-	9.1	-	9.9	-	9.6	-
	SD	6.7	-	4.0	-	5.5	-	5.2	-
	Median	10.0	-	9.0	-	9.5	-	10.0	-
	Minimum	2.0	-	3.0	-	2.0	-	0.0	-
	Maximum	21.0	-	16.0	-	21.0	-	17.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0	0	0.0	1	6.7
	1 to 4 days	6	54.5	7	77.8	13	65.0	9	60.0
	5 to 7 days	5	45.5	2	22.2	7	35.0	5	33.3
	more than 7 days	0	0.0	0	0.0	0	0.0	0	0.0
Maximum number of looser	0 to 1	0	0.0	0	0.0	0	0.0	1	6.7
	2 to 4	1	9.1	7	77.8	8	40.0	3	20.0
	5 to 7	5	45.5	2	22.2	7	35.0	10	66.7
	more than 7	5	45.5	0	0.0	5	25.0	1	6.7
Duration of vomiting-days	0-1 day	5	45.5	2	22.2	7	35.0	7	46.7
	2 days	1	9.1	4	44.4	5	25.0	1	6.7
	3-5 days	3	27.3	3	33.3	6	30.0	7	46.7
	more than 5 days	2	18.2	0	0.0	2	10.0	0	0.0
Max number of episodes of vomiting /day	0	3	27.3	1	11.1	4	20.0	3	20.0
	1 to 3	4	36.4	4	44.4	8	40.0	4	26.7
	4 to 6	1	9.1	4	44.4	5	25.0	5	33.3
	more than 6	3	27.3	0	0.0	3	15.0	3	20.0
Duration of fever-days	0 day	8	72.7	5	55.6	13	65.0	9	60.0
	1-2 days	1	9.1	3	33.3	4	20.0	5	33.3
	3-4 days	1	9.1	1	11.1	2	10.0	1	6.7
	more than 4 days	1	9.1	0	0.0	1	5.0	0	0.0
Maximum fever reported/day	less than 38.0°C	8	72.7	5	55.6	13	65.0	9	60.0
	38.0 to 338.2°C	1	9.1	2	22.2	3	15.0	3	20.0
	38.3 to 38.7°C	0	0.0	1	11.1	1	5.0	1	6.7
	more than 38.7°C	2	18.2	1	11.1	3	15.0	2	13.3
Duration of behavioural symptoms	0 day	3	27.3	2	22.2	5	25.0	4	26.7
	1-2 days	3	27.3	4	44.4	7	35.0	4	26.7
	3-4 days	1	9.1	2	22.2	3	15.0	3	20.0
	more than 4 days	4	36.4	1	11.1	5	25.0	4	26.7
Behavioural symptoms	Behave as usual	3	27.3	2	22.2	5	25.0	4	26.7
	Irritable/Less playful	0	0.0	0	0.0	0	0.0	1	6.7
	Lethargic/listless	8	72.7	6	66.7	14	70.0	10	66.7
	Seizures	0	0.0	1	11.1	1	5.0	0	0.0

N = number of RV GE (G9 serotype) 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 67 Characteristics of the RV GE episodes (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 by G12 serotype (ATP cohort for efficacy)

		HRV_2D N = 20		HRV_3D N = 14		HRV_POOL N = 34		Placebo N = 31	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	8.4	-	12.4	-	10.0	-	10.3	-
	SD	3.8	-	5.6	-	4.9	-	5.5	-
	Median	8.0	-	11.5	-	9.5	-	10.0	-
	Minimum	2.0	-	3.0	-	2.0	-	0.0	-
	Maximum	17.0	-	21.0	-	21.0	-	22.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0	0	0.0	1	3.2
	1 to 4 days	17	85.0	8	57.1	25	73.5	20	64.5
	5 to 7 days	3	15.0	5	35.7	8	23.5	8	25.8
	more than 7 days	0	0.0	1	7.1	1	2.9	2	6.5
Maximum number of looser	0 to 1	0	0.0	0	0.0	0	0.0	1	3.2
	2 to 4	6	30.0	3	21.4	9	26.5	12	38.7
	5 to 7	6	30.0	5	35.7	11	32.4	15	48.4
	more than 7	8	40.0	6	42.9	14	41.2	3	9.7
Duration of vomiting-days	0-1 day	9	45.0	4	28.6	13	38.2	13	41.9
	2 days	6	30.0	2	14.3	8	23.5	3	9.7
	3-5 days	5	25.0	8	57.1	13	38.2	13	41.9
	more than 5 days	0	0.0	0	0.0	0	0.0	2	6.5
Max number of episodes of vomiting /day	0	4	20.0	2	14.3	6	17.6	4	12.9
	1 to 3	6	30.0	4	28.6	10	29.4	12	38.7
	4 to 6	8	40.0	3	21.4	11	32.4	10	32.3
	more than 6	2	10.0	5	35.7	7	20.6	5	16.1
Duration of fever-days	0 day	15	75.0	7	50.0	22	64.7	15	48.4
	1-2 days	5	25.0	3	21.4	8	23.5	9	29.0
	3-4 days	0	0.0	3	21.4	3	8.8	5	16.1
	more than 4 days	0	0.0	1	7.1	1	2.9	2	6.5
Maximum fever reported/day	less than 38.0°C	15	75.0	7	50.0	22	64.7	15	48.4
	38.0 to 338.2°C	2	10.0	2	14.3	4	11.8	6	19.4
	38.3 to 38.7°C	3	15.0	1	7.1	4	11.8	5	16.1
	more than 38.7°C	0	0.0	4	28.6	4	11.8	5	16.1
Duration of behavioural symptoms	0 day	7	35.0	2	14.3	9	26.5	6	19.4
	1-2 days	8	40.0	2	14.3	10	29.4	15	48.4
	3-4 days	4	20.0	6	42.9	10	29.4	3	9.7
	more than 4 days	1	5.0	4	28.6	5	14.7	7	22.6
Behavioural symptoms	Behave as usual	7	35.0	2	14.3	9	26.5	6	19.4
	Irritable/Less playful	0	0.0	0	0.0	0	0.0	4	12.9
	Lethargic/listless	13	65.0	12	85.7	25	73.5	20	64.5
	Seizures	0	0.0	0	0.0	0	0.0	1	3.2

N = number of RV GE (G12 serotype) 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 68 Characteristics of the GE episodes (based on Clark scale) reported from 2 weeks after Dose 3 up to visit 6 (ATP cohort for efficacy)

		HRV_2D N = 772		HRV_3D N = 646		HRV_POOL N = 1418		Placebo N = 773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Clark severity score	Mean	6.4	-	6.6	-	6.5	-	7.3	-
	SD	4.5	-	4.7	-	4.6	-	4.6	-
	Median	5.0	-	5.0	-	5.0	-	7.0	-
	Minimum	0.0	-	0.0	-	0.0	-	0.0	-
	Maximum	23.0	-	23.0	-	23.0	-	22.0	-
Duration of looser than normal stools (days)	0 day	39	5.1	24	3.7	63	4.4	25	3.2
	1 to 4 days	521	67.5	440	68.1	961	67.8	518	67.0
	5 to 7 days	154	19.9	140	21.7	294	20.7	176	22.8
	more than 7 days	58	7.5	42	6.5	100	7.1	54	7.0
Maximum number of looser	0 to 1	39	5.1	25	3.9	64	4.5	25	3.2
	2 to 4	316	40.9	270	41.8	586	41.3	300	38.8
	5 to 7	298	38.6	261	40.4	559	39.4	340	44.0
	more than 7	119	15.4	90	13.9	209	14.7	108	14.0
Duration of vomiting-days	0-1 day	584	75.6	465	72.0	1049	74.0	506	65.5
	2 days	75	9.7	79	12.2	154	10.9	107	13.8
	3-5 days	87	11.3	78	12.1	165	11.6	132	17.1
	more than 5 days	26	3.4	24	3.7	50	3.5	28	3.6
Max number of episodes of vomiting /day	0	447	57.9	339	52.5	786	55.4	344	44.5
	1 to 3	194	25.1	184	28.5	378	26.7	248	32.1
	4 to 6	102	13.2	94	14.6	196	13.8	134	17.3
	more than 6	29	3.8	29	4.5	58	4.1	47	6.1
Duration of fever-days	0 day	544	70.5	461	71.4	1005	70.9	496	64.2
	1-2 days	190	24.6	144	22.3	334	23.6	218	28.2
	3-4 days	28	3.6	27	4.2	55	3.9	46	6.0
	more than 4 days	10	1.3	14	2.2	24	1.7	13	1.7
Maximum fever reported/day	less than 38.0°C	544	70.5	461	71.4	1005	70.9	496	64.2
	38.0 to 338.2°C	74	9.6	50	7.7	124	8.7	88	11.4
	38.3 to 38.7°C	47	6.1	58	9.0	105	7.4	88	11.4
	more than 38.7°C	107	13.9	77	11.9	184	13.0	101	13.1
Duration of behavioural symptoms	0 day	450	58.3	360	55.7	810	57.1	387	50.1
	1-2 days	205	26.6	169	26.2	374	26.4	239	30.9
	3-4 days	67	8.7	60	9.3	127	9.0	86	11.1
	more than 4 days	50	6.5	57	8.8	107	7.5	61	7.9
Behavioural symptoms	Behave as usual	450	58.3	360	55.7	810	57.1	387	50.1
	Irritable/Less playful	62	8.0	65	10.1	127	9.0	79	10.2
	Lethargic/listless	254	32.9	215	33.3	469	33.1	301	38.9
	Seizures	6	0.8	6	0.9	12	0.8	6	0.8

N = number of 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 69 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to visit 6 - (ATP cohort for efficacy)

		HRV_2D N = 1496	HRV_3D N = 1478	HRV_POOL N = 2974	Placebo N = 1443
Characteristics	Parameters or Categories	Value or n	Value or n	Value or n	Value or n
Duration in years	Sum	946.9	928.8	1876	902.6
	Mean	0.63	0.63	0.63	0.63
	Minimum	0.01	0.01	0.01	0.01
	Q1	0.63	0.62	0.63	0.62
	Median	0.65	0.65	0.65	0.65
	Q3	0.67	0.67	0.67	0.67
	Maximum	1.33	2.06	2.06	1.26

N = number of subject included in each group
Sum = sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 70 Duration (in years) of efficacy follow-up period - from 2 weeks after Dose 3 up to visit 6 - Cohort 1 (ATP cohort for efficacy)

	HRV_2D N = 553	HRV_3D N = 548	HRV_POOL N = 1101	Placebo N = 552
Duration (years) of follow-up period	Value or n	Value or n	Value or n	Value or n
Sum	347.9	344.9	692.8	344.4
Mean	0.63	0.63	0.63	0.62
Minimum	0.01	0.02	0.01	0.01
Q1	0.63	0.62	0.62	0.62
Median	0.65	0.65	0.65	0.65
Q3	0.67	0.67	0.67	0.67
Maximum	1.33	2.06	2.06	1.26

N = number of subject included in each group
Sum= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 71 Duration (in years) of efficacy follow-up period - from 2 weeks after Dose 3 up to visit 6 - Cohort 2 South Africa (ATP cohort for efficacy)

	HRV_2D N = 418	HRV_3D N = 425	HRV_POOL N = 843	Placebo N = 408
Duration (years) of follow-up period	Value or n	Value or n	Value or n	Value or n
Sum	269.0	267.5	536.5	257.2
Mean	0.64	0.63	0.64	0.63
Minimum	0.05	0.01	0.01	0.05
Q1	0.63	0.63	0.63	0.63
Median	0.65	0.65	0.65	0.65
Q3	0.67	0.67	0.67	0.67
Maximum	0.90	0.76	0.90	0.81

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 72 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to visit 6 - South Africa (ATP cohort for efficacy)

	HRV_2D N = 971	HRV_3D N = 973	HRV_POOL N = 1944	Placebo N = 960
Duration (years) of follow-up period	Value or n	Value or n	Value or n	Value or n
Sum	616.9	612.4	1229	601.6
Mean	0.64	0.63	0.63	0.63
Minimum	0.01	0.01	0.01	0.01
Q1	0.63	0.62	0.63	0.62
Median	0.65	0.65	0.65	0.65
Q3	0.67	0.67	0.67	0.67
Maximum	1.33	2.06	2.06	1.26

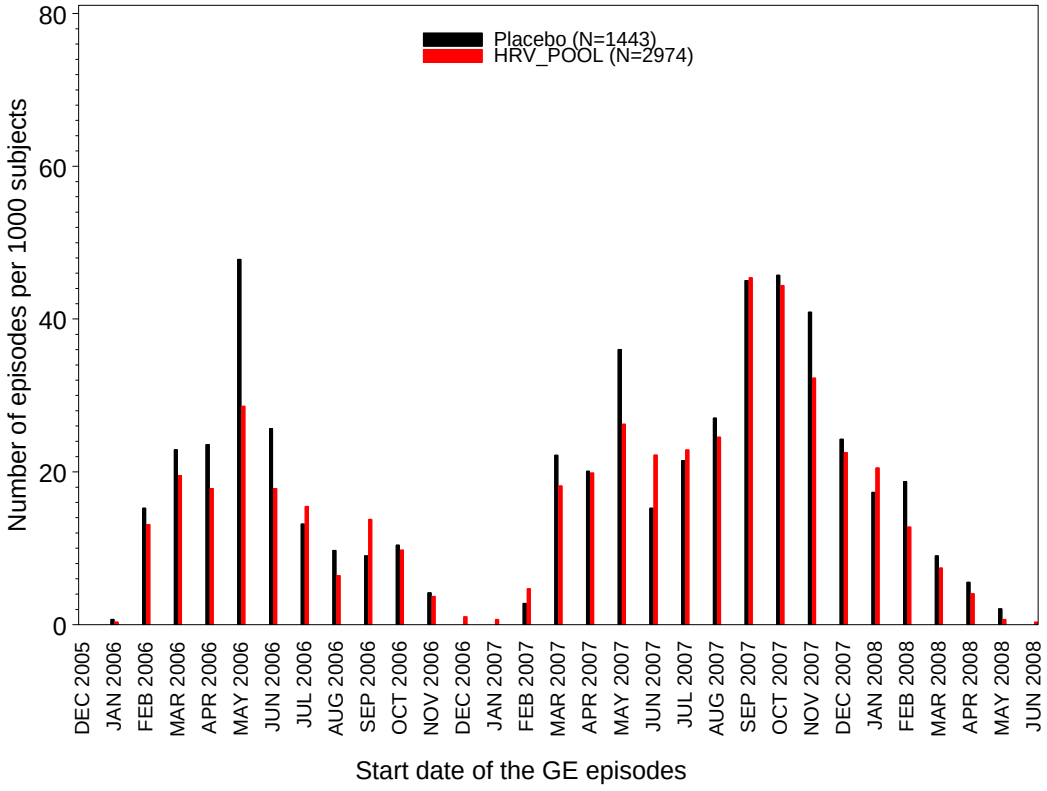
N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 73 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to visit 6 - Malawi (ATP cohort for efficacy)

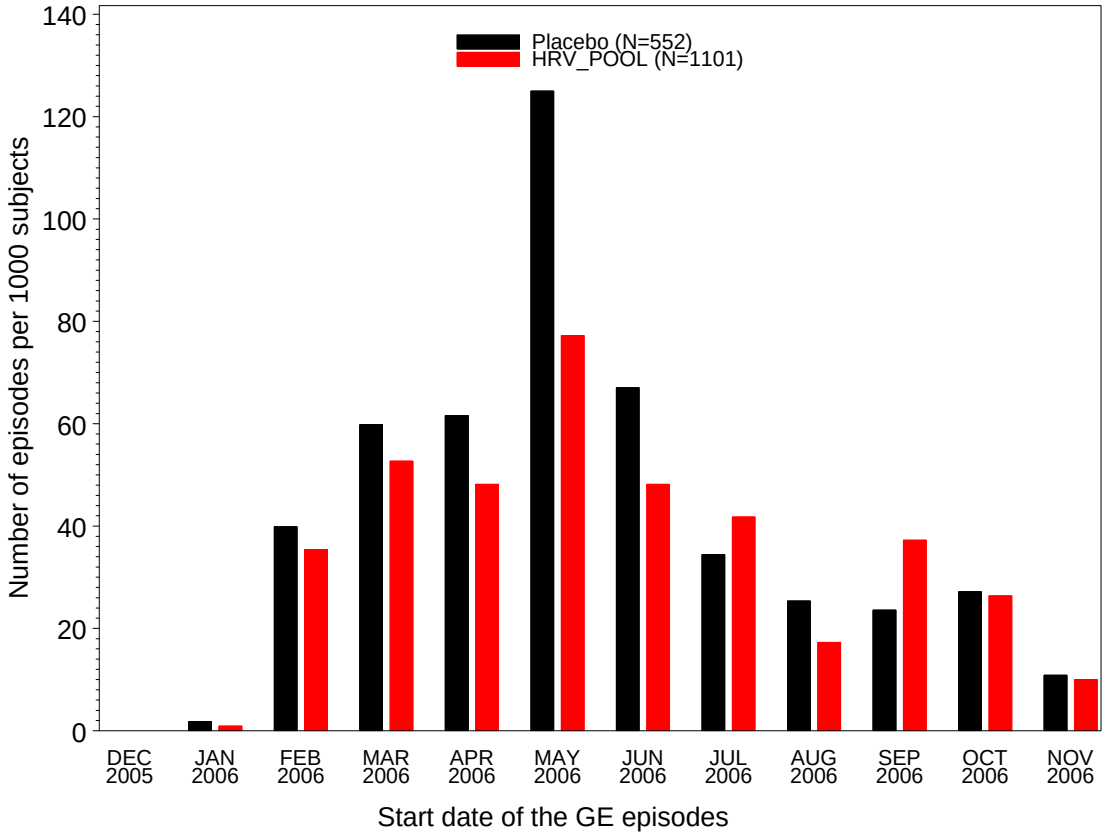
	HRV_2D N = 525	HRV_3D N = 505	HRV_POOL N = 1030	Placebo N = 483
Duration (years) of follow-up period	Value or n	Value or n	Value or n	Value or n
Sum	330.0	316.4	646.4	301.0
Mean	0.63	0.63	0.63	0.62
Minimum	0.03	0.01	0.01	0.03
Q1	0.63	0.62	0.63	0.62
Median	0.64	0.64	0.64	0.64
Q3	0.65	0.65	0.65	0.66
Maximum	0.96	0.96	0.96	1.04

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

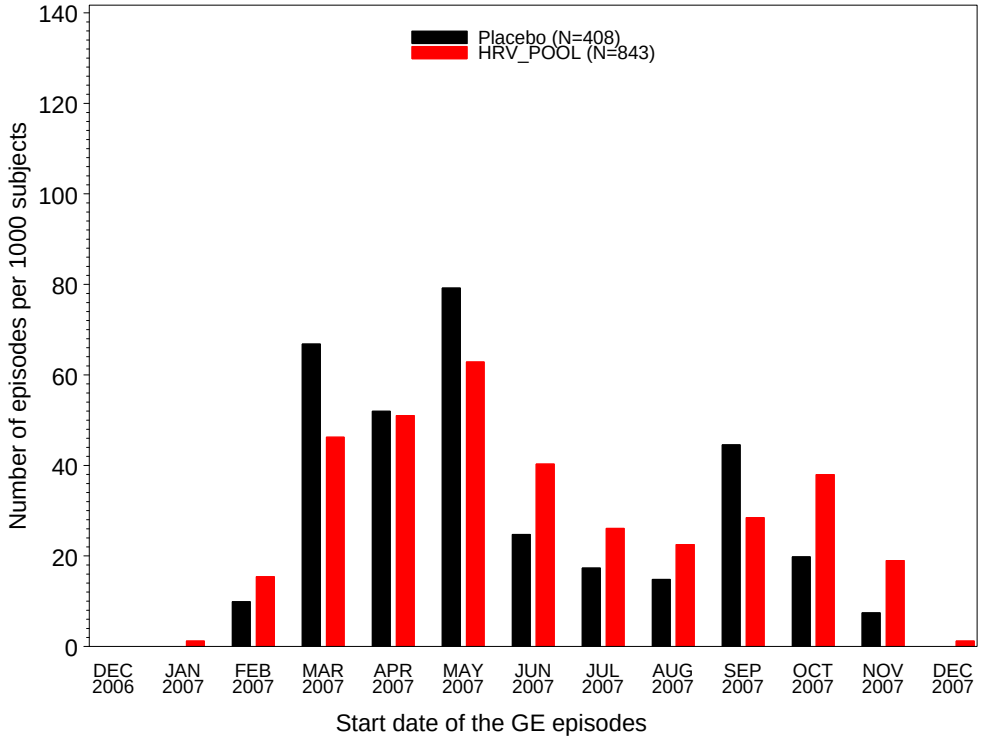
Supplement 74 Seasonal distribution of GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group (ATP cohort for efficacy)



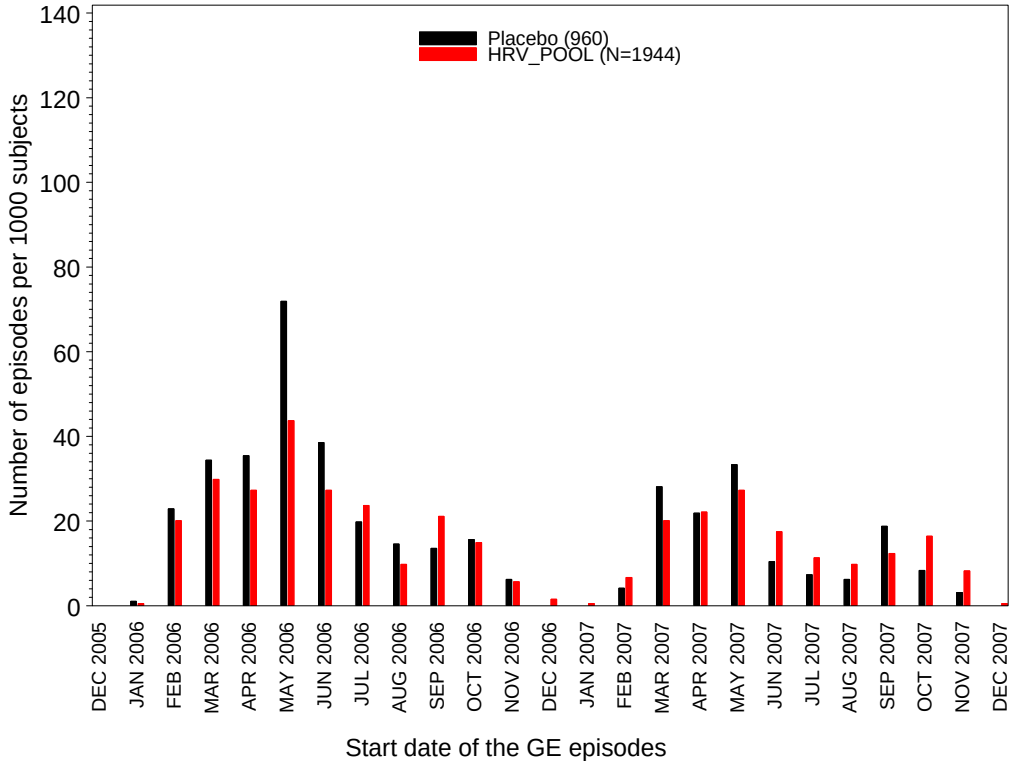
Supplement 75 Seasonal distribution of GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – Cohort 1 South Africa (ATP cohort for efficacy)



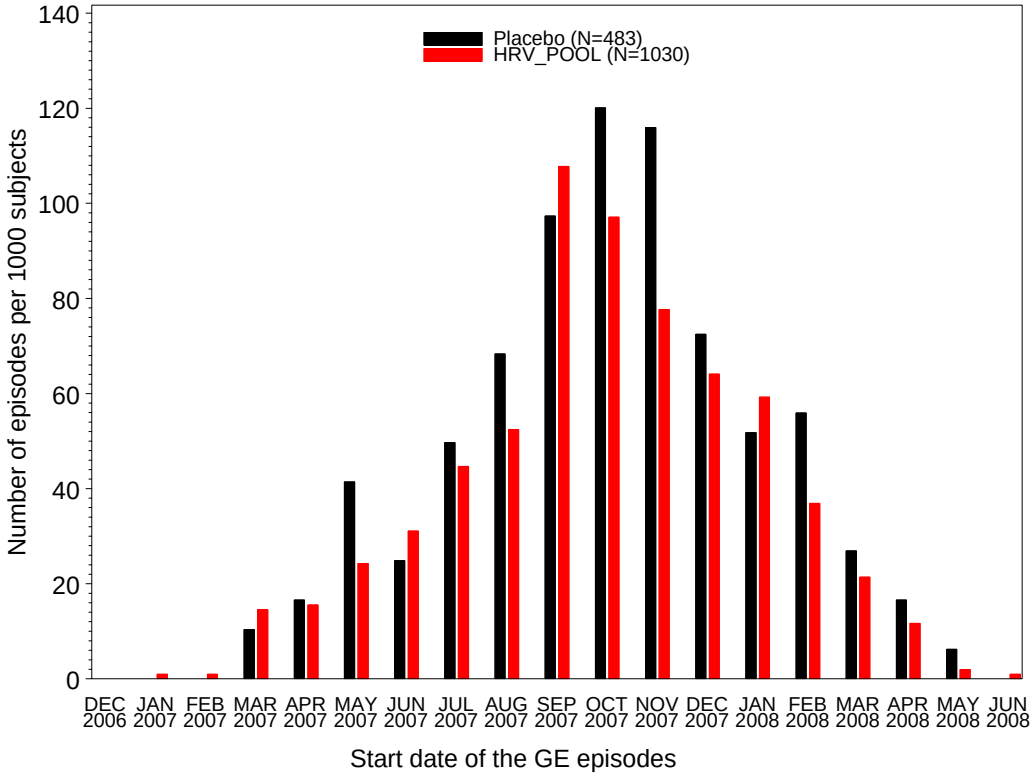
Supplement 76 Seasonal distribution of GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – Cohort 2 South Africa (ATP cohort for efficacy)



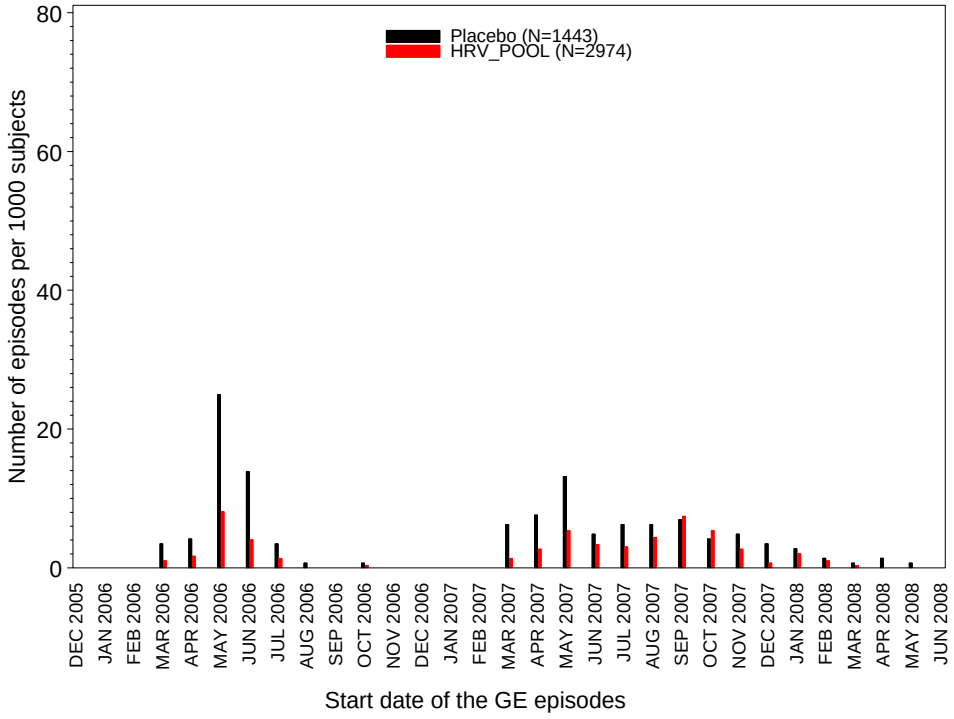
Supplement 77 Seasonal distribution of GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – South Africa (ATP cohort for efficacy)



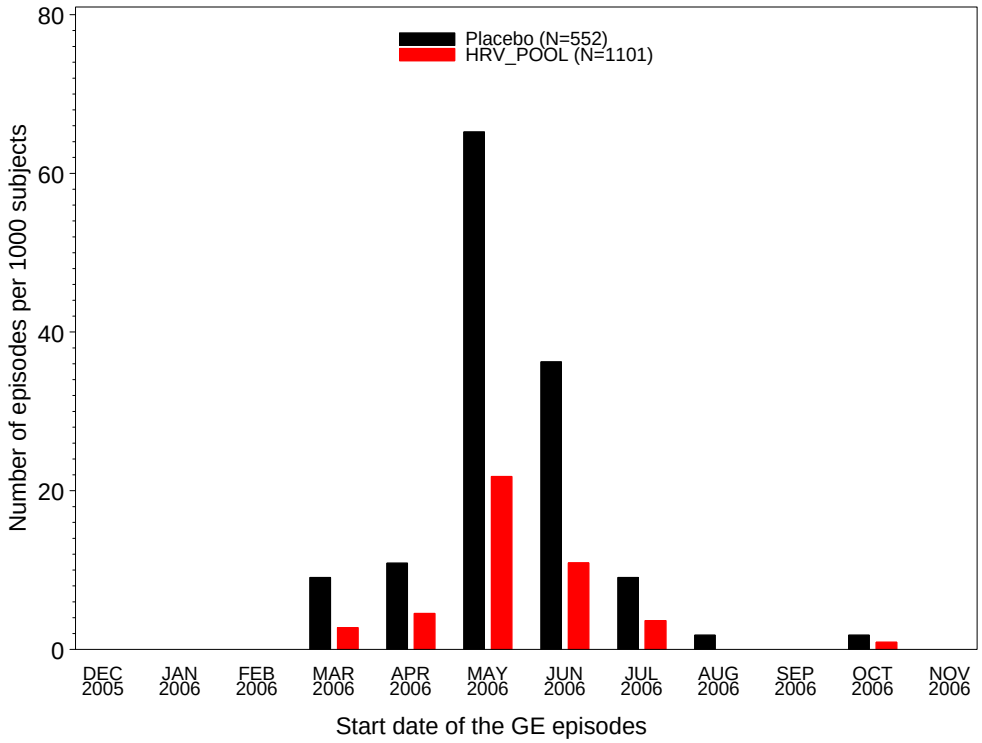
Supplement 78 Seasonal distribution of GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – Malawi (ATP cohort for efficacy)



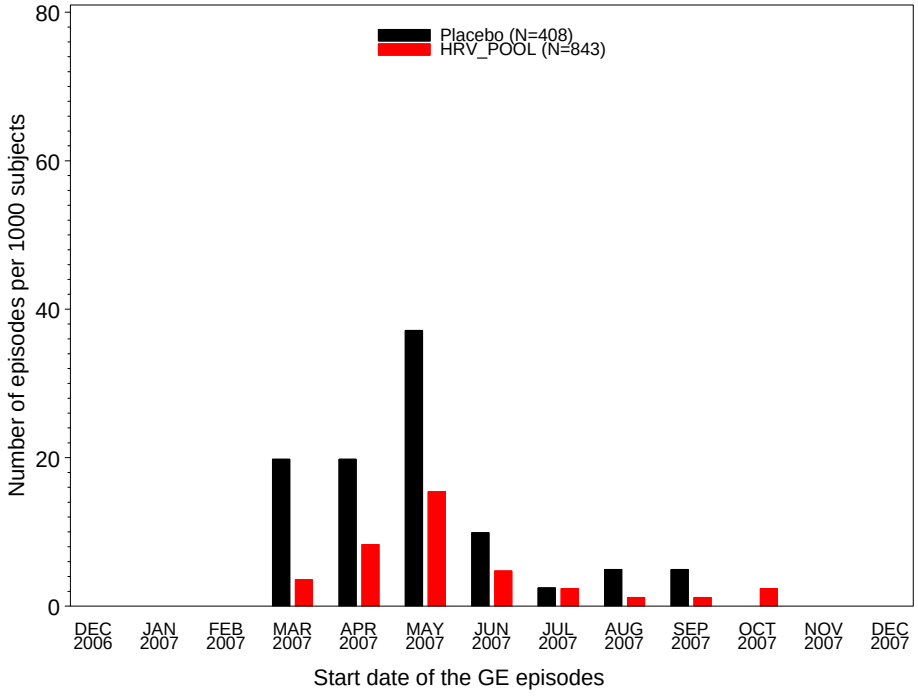
Supplement 79 Seasonal distribution of RV GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group (ATP cohort for efficacy)



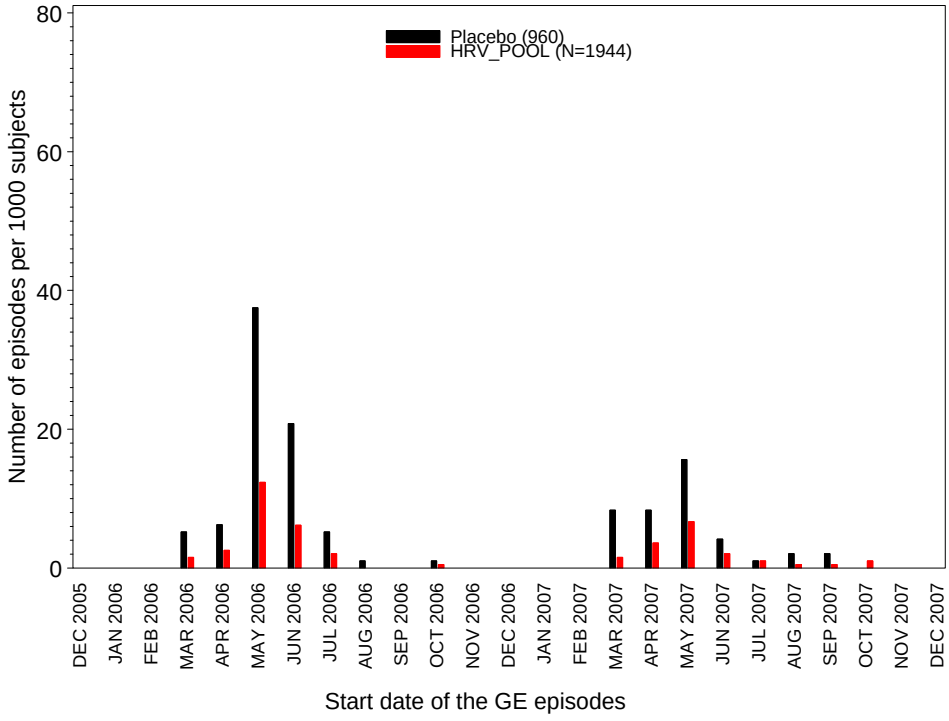
Supplement 80 Seasonal distribution of RV GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – Cohort 1 South Africa (ATP cohort for efficacy)



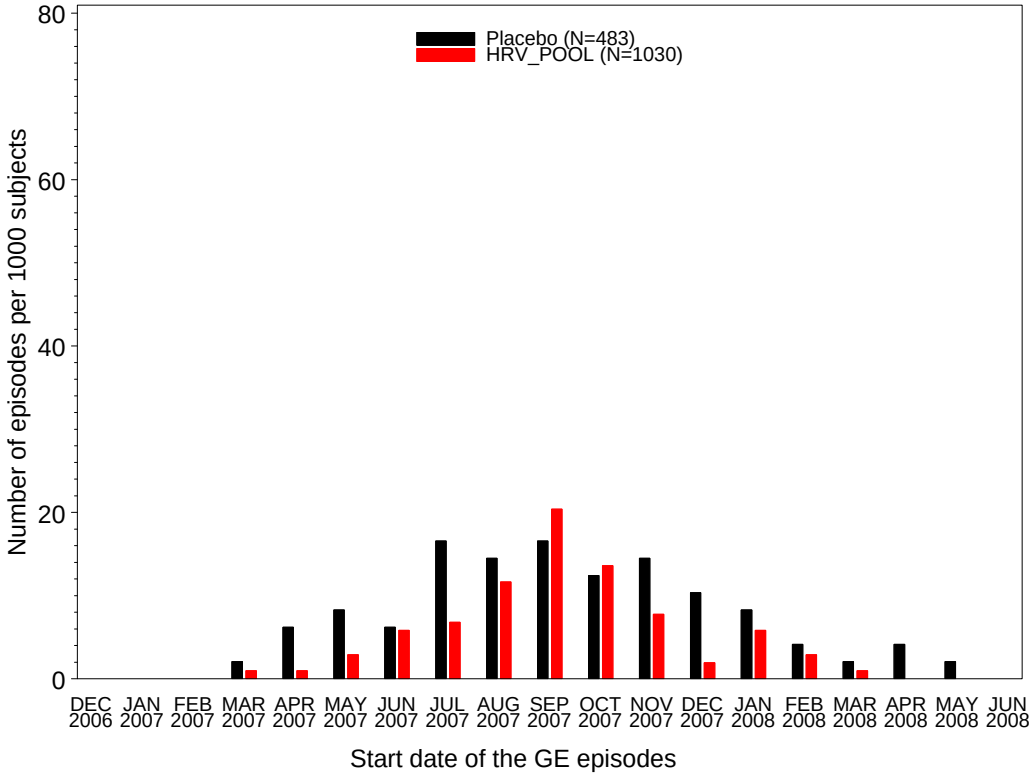
Supplement 81 Seasonal distribution of RV GE episode reported from 2 weeks after dose 3 up to VISIT 6 for pooled HRV groups and placebo group – Cohort 2 South Africa (ATP cohort for efficacy)



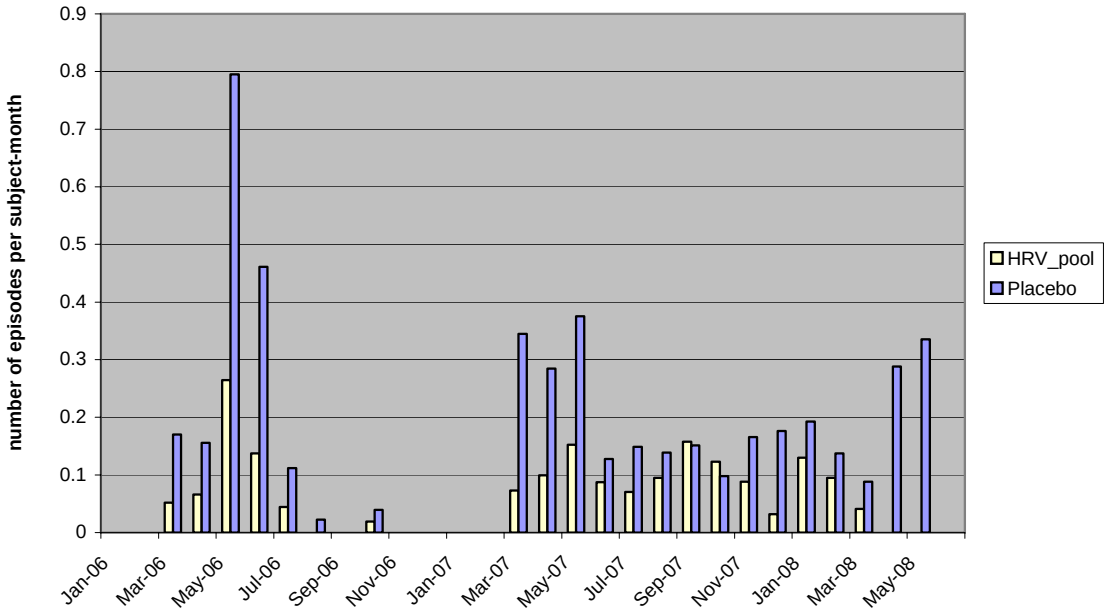
Supplement 82 Seasonal distribution of RV GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – South Africa (ATP cohort for efficacy)



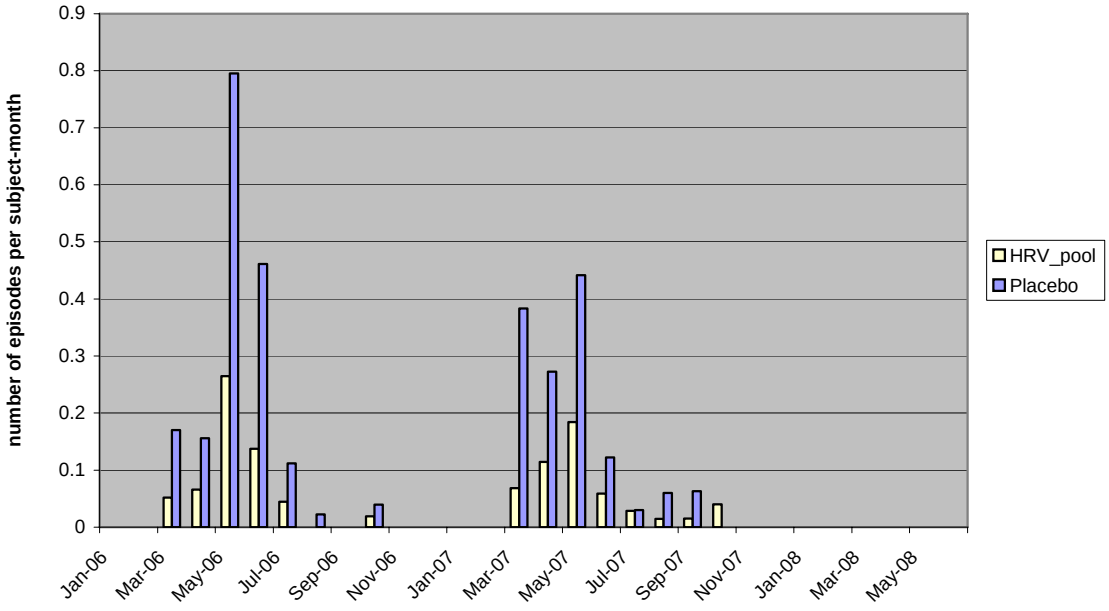
Supplement 83 Seasonal distribution of RV GE episode reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – Malawi (ATP cohort for efficacy)



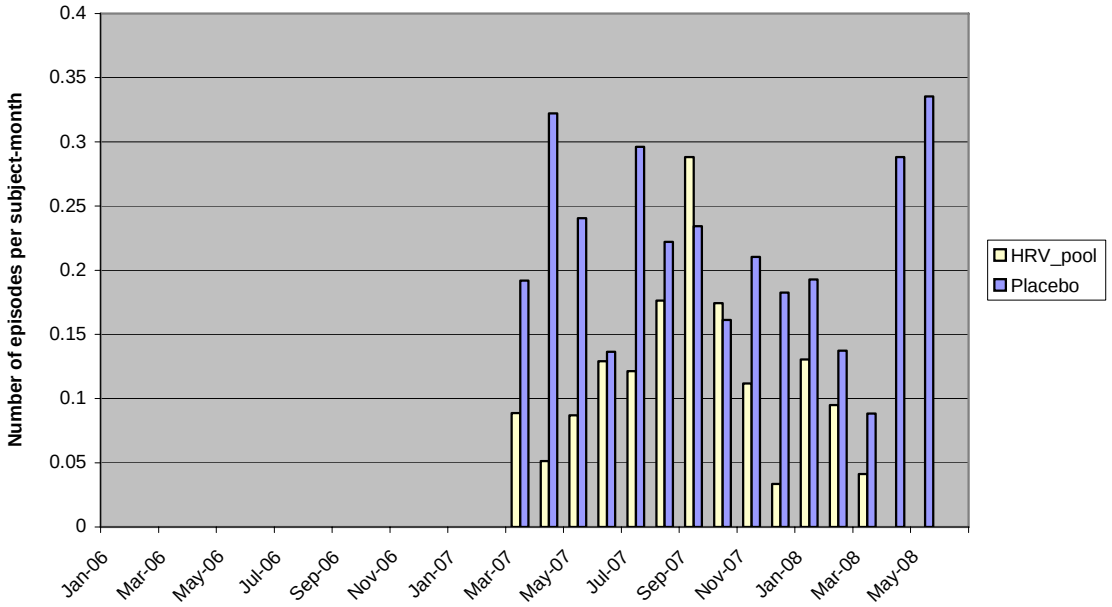
Supplement 84 Seasonal distribution of RV GE episode reported from 2 weeks after dose 3 up to Visit 6 for pooled HRV groups and placebo group (ATP cohort for efficacy)



Supplement 85 Seasonal distribution of RV GE episode reported from 2 weeks after dose 3 up to VISIT 6 for pooled HRV groups and placebo group (ATP cohort for efficacy, South Africa)



Supplement 86 Seasonal distribution of RV GE episode reported from 2 weeks after dose 3 up to VISIT 6 for pooled HRV groups and placebo group (ATP cohort for efficacy, Malawi)



Supplement 87 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by South Africa cohorts (ATP cohort for efficacy)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	553	4	0.7	0.2	1.8	82.6	49.2	95.6	<0.001
	HRV_3D	548	5	0.9	0.3	2.1	78.1	41.1	93.5	<0.001
	HRV_POOL	1101	9	0.8	0.4	1.5	80.4	56.0	92.0	<0.001
	Placebo	552	23	4.2	2.7	6.2	-	-	-	-
2	HRV_2D	418	5	1.2	0.4	2.8	45.8	-80.2	85.7	0.292
	HRV_3D	425	1	0.2	0.0	1.3	89.3	23.0	99.8	0.010
	HRV_POOL	843	6	0.7	0.3	1.5	67.7	-1.5	90.5	0.048
	Placebo	408	9	2.2	1.0	4.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 88 Percentage of subjects reporting RVGE episode with score equal to or greater than 11 on Vesikari scale and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
≥11	HRV_2D	1496	30	2.0	1.4	2.9	58.7	35.7	74.0	<0.001
	HRV_3D	1478	26	1.8	1.2	2.6	63.7	42.4	77.8	<0.001
	HRV_POOL	2974	56	1.9	1.4	2.4	61.2	44.0	73.2	<0.001
	Placebo	1443	70	4.9	3.8	6.1	-	-	-	-
≥12	HRV_2D	1496	21	1.4	0.9	2.1	54.0	20.9	74.0	0.002
	HRV_3D	1478	20	1.4	0.8	2.1	55.6	23.1	75.2	0.002
	HRV_POOL	2974	41	1.4	1.0	1.9	54.8	29.2	71.2	<0.001
	Placebo	1443	44	3.0	2.2	4.1	-	-	-	-
≥13	HRV_2D	1496	19	1.3	0.8	2.0	50.5	11.6	73.1	0.014
	HRV_3D	1478	12	0.8	0.4	1.4	68.3	37.9	85.0	<0.001
	HRV_POOL	2974	31	1.0	0.7	1.5	59.3	32.7	75.6	<0.001
	Placebo	1443	37	2.6	1.8	3.5	-	-	-	-
≥14	HRV_2D	1496	14	0.9	0.5	1.6	35.7	-32.6	69.8	0.234
	HRV_3D	1478	9	0.6	0.3	1.2	58.2	4.7	83.1	0.027
	HRV_POOL	2974	23	0.8	0.5	1.2	46.9	-1.0	71.9	0.036
	Placebo	1443	21	1.5	0.9	2.2	-	-	-	-
≥15	HRV_2D	1496	8	0.5	0.2	1.1	48.6	-29.3	81.1	0.144
	HRV_3D	1478	7	0.5	0.2	1.0	54.4	-18.7	84.3	0.089
	HRV_POOL	2974	15	0.5	0.3	0.8	51.5	-6.5	77.9	0.051
	Placebo	1443	15	1.0	0.6	1.7	-	-	-	-
≥16	HRV_2D	1496	8	0.5	0.2	1.1	14.3	-150.4	71.2	0.811
	HRV_3D	1478	4	0.3	0.1	0.7	56.6	-55.5	90.2	0.174
	HRV_POOL	2974	12	0.4	0.2	0.7	35.3	-73.8	75.0	0.353
	Placebo	1443	9	0.6	0.3	1.2	-	-	-	-
≥17	HRV_2D	1496	4	0.3	0.1	0.7	35.7	-171.2	86.7	0.541
	HRV_3D	1478	2	0.1	0.0	0.5	67.5	-82.0	96.8	0.174
	HRV_POOL	2974	6	0.2	0.1	0.4	51.5	-81.5	87.0	0.223
	Placebo	1443	6	0.4	0.2	0.9	-	-	-	-
≥18	HRV_2D	1496	2	0.1	0.0	0.5	61.4	-135.7	96.3	0.280
	HRV_3D	1478	1	0.1	0.0	0.4	80.5	-74.5	99.6	0.120
	HRV_POOL	2974	3	0.1	0.0	0.3	70.9	-49.6	95.5	0.123
	Placebo	1443	5	0.3	0.1	0.8	-	-	-	-
≥19	HRV_2D	1496	1	0.1	0.0	0.4	51.8	-826.4	99.2	0.618
	HRV_3D	1478	1	0.1	0.0	0.4	51.2	-837.7	99.2	0.620
	HRV_POOL	2974	2	0.1	0.0	0.2	51.5	-569.4	96.5	0.601
	Placebo	1443	2	0.1	0.0	0.5	-	-	-	-
≥20	HRV_2D	1496	0	0.0	0.0	0.2	.	.	.	-
	HRV_3D	1478	0	0.0	0.0	0.2	.	.	.	-
	HRV_POOL	2974	0	0.0	0.0	0.1	.	.	.	-
	Placebo	1443	0	0.0	0.0	0.3	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least one RV GE episode with Vesikari score ≥11 in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 89 Percentage of subject reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by Cox (ATP cohort for efficacy)

					Person-year rate			VE			
Event Type	Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any	HRV_POOL	2974	56	1857.43	0.0301	0.0232	0.0392	62.141	46.200	73.358	<0.0001
	Placebo	1443	70	877.34	0.0798	0.0631	0.1008	-	-	-	.

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 90 Percentage of subject reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by Cox (ATP cohort for efficacy, South Africa)

					Person-year rate			VE			
Event Type	Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any	HRV_POOL	1944	15	1223.49	0.0123	0.0074	0.0203	77.277	58.042	87.694	<0.0001
	Placebo	960	32	587.87	0.0544	0.0385	0.0770	-	-	-	.

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 91 Percentage of subject reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by Cox (ATP cohort for efficacy, Malawi)

					Person-year rate			VE			
Event Type	Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any	HRV_POOL	1030	41	633.94	0.0647	0.0476	0.0878	50.841	23.564	68.383	0.0016
	Placebo	483	38	289.48	0.1313	0.0955	0.1804	-	-	-	.

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 92 Percentage of subject reporting severe RV GE episodes and risk difference of the vaccines from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

					Person-year rate			Risk Difference (Placebo-HRV)		
Event Type	Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
Severe RV GE of any type										
Any	HRV_2D	1496	30	936.57	0.032	0.022	0.046	0.0478	0.0261	0.0709
	HRV_3D	1478	26	920.86	0.028	0.019	0.041	0.0516	0.0303	0.0745
	HRV_POOL	2974	56	1857.43	0.030	0.023	0.039	0.0496	0.0307	0.0718
	Placebo	1443	70	877.34	0.080	0.063	0.101	-	-	-
Severe RV GE of G1 wild type										
Any	HRV_2D	1496	8	943.88	0.008	0.004	0.017	0.0173	0.0052	0.0309
	HRV_3D	1478	9	926.20	0.010	0.005	0.019	0.0160	0.0036	0.0298
	HRV_POOL	2974	17	1870.08	0.009	0.006	0.015	0.0166	0.0064	0.0301
	Placebo	1443	23	893.73	0.026	0.017	0.039	-	-	-
Severe RV GE of pooled Non G1 (G2, G3,...)										
Any	HRV_2D	1496	22	939.59	0.023	0.015	0.036	0.0296	0.0117	0.0489
	HRV_3D	1478	17	923.41	0.018	0.011	0.030	0.0346	0.0173	0.0535
	HRV_POOL	2974	39	1863.01	0.021	0.015	0.029	0.0321	0.0168	0.0505
	Placebo	1443	47	886.18	0.053	0.040	0.071	-	-	-

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) and CI method.

Supplement 93 Percentage of subject reporting severe RV GE episodes and risk difference of the vaccines from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy, South Africa)

					Person-year rate			Risk differences (Placebo - HRV)		
Event Type	Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
Severe RV GE of any type										
Any	HRV_2D	971	9	613.23	0.015	0.008	0.028	0.0398	0.0188	0.0634
	HRV_3D	973	6	610.26	0.010	0.004	0.022	0.0446	0.0246	0.0678
	HRV_POOL	1944	15	1223.49	0.012	0.007	0.020	0.0422	0.0243	0.0652
	Placebo	960	32	587.87	0.054	0.038	0.077	-	-	-
Severe RV GE of G1 wild type										
Any	HRV_2D	971	6	614.58	0.010	0.004	0.022	0.0205	0.0041	0.0391
	HRV_3D	973	5	610.35	0.008	0.003	0.020	0.0221	0.0061	0.0405
	HRV_POOL	1944	11	1224.93	0.009	0.005	0.016	0.0213	0.0080	0.0396
	Placebo	960	18	594.03	0.030	0.019	0.048	-	-	-
Severe RV GE of pooled Non G1 (G2, G3,...)										
Any	HRV_2D	971	3	615.52	0.005	0.002	0.015	0.0186	0.0046	0.0352
	HRV_3D	973	1	612.30	0.002	0.000	0.012	0.0219	0.0081	0.0381
	HRV_POOL	1944	4	1227.82	0.003	0.001	0.009	0.0203	0.0092	0.0366
	Placebo	960	14	595.43	0.024	0.014	0.040	-	-	-

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 differences (Placebo – HRV) and CI method.

Supplement 94 Percentage of subject reporting severe RV GE episodes and risk difference of the vaccines from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy, Malawi)

					Person-year rate			Risk differences (Placebo - HRV)		
Event Type	Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
Severe RV GE of any type										
Any	HRV_2D	525	21	323.34	0.065	0.042	0.100	0.0663	0.0165	0.1204
	HRV_3D	505	20	310.60	0.064	0.042	0.100	0.0669	0.0166	0.1211
	HRV_POOL	1030	41	633.94	0.065	0.048	0.088	0.0666	0.0240	0.1186
	Placebo	483	38	289.48	0.131	0.096	0.180	-	-	-
Severe RV GE of G1 wild type										
Any	HRV_2D	525	2	329.30	0.006	0.002	0.024	0.0106	-0.0100	0.0344
	HRV_3D	505	4	315.85	0.013	0.005	0.034	0.0040	-0.0192	0.0287
	HRV_POOL	1030	6	645.15	0.009	0.004	0.021	0.0074	-0.0076	0.0313
	Placebo	483	5	299.71	0.017	0.007	0.040	-	-	-
Severe RV GE of pooled Non G1 (G2, G3,...)										
Any	HRV_2D	525	19	324.07	0.059	0.037	0.092	0.0549	0.0106	0.1057
	HRV_3D	505	16	311.11	0.051	0.032	0.084	0.0621	0.0159	0.1023
	HRV_POOL	1030	35	635.18	0.055	0.040	0.077	0.0584	0.0191	0.1071
	Placebo	483	33	290.76	0.113	0.081	0.160	-	-	-

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 differences (Placebo – HRV) and CI method

Supplement 95 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks after dose 3) before /after beginning of RV season in South Africa (ATP cohort for efficacy)

				n/N			VE			
	Group	N	n	%	LL	UL	%	LL	UL	P-value
Vaccination completed after RV season start	HRV_2D	493	4	0.8	0.2	2.1	66.7	-9.8	92.2	0.047
	HRV_3D	505	3	0.6	0.1	1.7	75.6	9.7	95.6	0.019
	HRV_POOL	998	7	0.7	0.3	1.4	71.2	20.8	90.4	0.011
	Placebo	492	12	2.4	1.3	4.2	-	-	-	-
Vaccination completed before RV season start	HRV_2D	478	5	1.0	0.3	2.4	75.5	32.8	92.8	0.002
	HRV_3D	468	3	0.6	0.1	1.9	85.0	49.4	97.1	<0.001
	HRV_POOL	946	8	0.8	0.4	1.7	80.2	53.1	92.5	<0.001
	Placebo	468	20	4.3	2.6	6.5	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test
RV season starts at 1st of March in South Africa

Supplement 96 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by country (ATP cohort for efficacy)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	525	45	8.6	6.3	11.3	32.1	-1.4	54.9	0.040
	HRV_3D	505	40	7.9	5.7	10.6	37.3	5.0	59.0	0.016
	HRV_POOL	1030	85	8.3	6.6	10.1	34.7	7.7	53.5	0.009
	Placebo	483	61	12.6	9.8	15.9	-	-	-	-
South Africa	HRV_2D	971	48	4.9	3.7	6.5	58.0	40.6	70.7	<0.001
	HRV_3D	973	34	3.5	2.4	4.8	70.3	56.1	80.4	<0.001
	HRV_POOL	1944	82	4.2	3.4	5.2	64.2	52.0	73.4	<0.001
	Placebo	960	113	11.8	9.8	14.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 97 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by South Africa cohort (ATP cohort for efficacy)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	553	28	5.1	3.4	7.2	61.7	40.1	76.2	<0.001
	HRV_3D	548	21	3.8	2.4	5.8	71.0	52.4	83.1	<0.001
	HRV_POOL	1101	49	4.5	3.3	5.8	66.3	51.0	77.1	<0.001
	Placebo	552	73	13.2	10.5	16.3	-	-	-	-
2	HRV_2D	418	20	4.8	2.9	7.3	51.2	14.5	73.0	0.007
	HRV_3D	425	13	3.1	1.6	5.2	68.8	40.5	84.7	<0.001
	HRV_POOL	843	33	3.9	2.7	5.5	60.1	35.1	75.6	<0.001
	Placebo	408	40	9.8	7.1	13.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 98 Percentage of subject reporting RV GE episodes and risk difference of the vaccines from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

					Person-year rate			Risk differences (Placebo - HRV)		
Event Type	Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
RV GE of any type										
Any	HRV_2D	1496	93	912.85	0.102	0.083	0.125	0.1070	0.0701	0.1453
	HRV_3D	1478	74	901.08	0.082	0.065	0.103	0.1267	0.0911	0.1641
	HRV_POOL	2974	167	1813.93	0.092	0.079	0.107	0.1168	0.0843	0.1527
	Placebo	1443	174	833.09	0.209	0.180	0.242	-	-	-
RV GE of G1 wild type										
Any	HRV_2D	1496	31	934.02	0.033	0.023	0.047	0.0564	0.0337	0.0808
	HRV_3D	1478	22	921.55	0.024	0.016	0.036	0.0657	0.0440	0.0894
	HRV_POOL	2974	53	1855.57	0.029	0.022	0.037	0.0610	0.0411	0.0843
	Placebo	1443	78	870.49	0.090	0.072	0.112	-	-	-
RV GE of pooled Non G1 (G2, G3,...)										
Any	HRV_2D	1496	62	925.73	0.067	0.052	0.086	0.0452	0.0175	0.0740
	HRV_3D	1478	51	908.78	0.056	0.043	0.074	0.0560	0.0291	0.0842
	HRV_POOL	2974	113	1834.51	0.062	0.051	0.074	0.0506	0.0268	0.0774
	Placebo	1443	97	864.81	0.112	0.092	0.137	-	-	-

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 differences (Placebo – HRV) and CI method

Supplement 99 Percentage of subject reporting RV GE episodes and risk difference of the vaccines from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy, South Africa)

					Person-year rate			Risk differences (Placebo - HRV)		
Event Type	Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
RV GE of any type										
Any	HRV_2D	971	48	597.23	0.080	0.061	0.107	0.1243	0.0810	0.1702
	HRV_3D	973	34	598.11	0.057	0.041	0.080	0.1478	0.1066	0.1923
	HRV_POOL	1944	82	1195.35	0.069	0.055	0.085	0.1361	0.0978	0.1796
	Placebo	960	113	552.08	0.205	0.170	0.246	-	-	-
RV GE of G1 wild type										
Any	HRV_2D	971	29	604.72	0.048	0.033	0.069	0.0726	0.0397	0.1079
	HRV_3D	973	17	605.75	0.028	0.017	0.045	0.0925	0.0619	0.1263
	HRV_POOL	1944	46	1210.48	0.038	0.028	0.051	0.0825	0.0542	0.1160
	Placebo	960	69	572.38	0.121	0.095	0.153	-	-	-
RV GE of pooled Non G1 (G2, G3,...)										
Any	HRV_2D	971	19	609.39	0.031	0.020	0.049	0.0445	0.0183	0.0729
	HRV_3D	973	17	604.75	0.028	0.017	0.045	0.0476	0.0217	0.0757
	HRV_POOL	1944	36	1214.14	0.030	0.021	0.041	0.0460	0.0235	0.0733
	Placebo	960	44	581.29	0.076	0.056	0.102	-	-	-

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 differences (Placebo – HRV) and CI method

Supplement 100 Percentage of subject reporting RV GE episodes and risk difference of the vaccines from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy, Malawi)

					Person-year rate			Risk differences (Placebo - HRV)		
Event Type	Group	N	n	T (year)	n/T	LL	UL	RD	LL	UL
RV GE of any type										
Any	HRV_2D	525	45	315.61	0.143	0.106	0.191	0.0745	0.0062	0.1462
	HRV_3D	505	40	302.97	0.132	0.097	0.180	0.0850	0.0171	0.1563
	HRV_POOL	1030	85	618.58	0.137	0.111	0.170	0.0797	0.0215	0.1469
	Placebo	483	61	281.01	0.217	0.169	0.279	-	-	-
RV GE of G1 wild type										
Any	HRV_2D	525	2	329.30	0.006	0.002	0.024	0.0241	0.0008	0.0523
	HRV_3D	505	5	315.79	0.016	0.007	0.038	0.0144	-0.0122	0.0437
	HRV_POOL	1030	7	645.10	0.011	0.005	0.023	0.0193	0.0006	0.0477
	Placebo	483	9	298.11	0.030	0.016	0.058	-	-	-
RV GE of pooled Non G1 (G2, G3,...)										
Any	HRV_2D	525	43	316.34	0.136	0.101	0.183	0.0510	-0.0137	0.1186
	HRV_3D	505	34	304.03	0.112	0.080	0.157	0.0751	0.0123	0.1411
	HRV_POOL	1030	77	620.38	0.124	0.099	0.155	0.0628	0.0089	0.1257
	Placebo	483	53	283.53	0.187	0.143	0.245	-	-	-

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 differences (Placebo – HRV) and CI method

Supplement 101 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by RV serotype (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV_2D	1496	31	2.1	1.4	2.9	61.7	41.2	75.6	<0.001
	HRV_3D	1478	22	1.5	0.9	2.2	72.5	55.3	83.7	<0.001
	HRV_POOL	2974	53	1.8	1.3	2.3	67.0	52.7	77.2	<0.001
	Placebo	1443	78	5.4	4.3	6.7	-	-	-	-
G2	HRV_2D	1496	14	0.9	0.5	1.6	43.7	-13.3	73.1	0.102
	HRV_3D	1478	17	1.2	0.7	1.8	30.8	-34.2	65.1	0.272
	HRV_POOL	2974	31	1.0	0.7	1.5	37.3	-11.6	64.4	0.084
	Placebo	1443	24	1.7	1.1	2.5	-	-	-	-
G3	HRV_2D	1496	7	0.5	0.2	1.0	38.6	-73.4	79.8	0.350
	HRV_3D	1478	1	0.1	0.0	0.4	91.1	38.9	99.8	0.003
	HRV_POOL	2974	8	0.3	0.1	0.5	64.7	3.7	87.7	0.026
	Placebo	1443	11	0.8	0.4	1.4	-	-	-	-
G8	HRV_2D	1496	15	1.0	0.6	1.6	37.1	-25.9	69.5	0.191
	HRV_3D	1478	13	0.9	0.5	1.5	44.8	-13.6	74.3	0.094
	HRV_POOL	2974	28	0.9	0.6	1.4	40.9	-7.4	67.2	0.071
	Placebo	1443	23	1.6	1.0	2.4	-	-	-	-
G9	HRV_2D	1496	11	0.7	0.4	1.3	29.3	-64.8	70.6	0.434
	HRV_3D	1478	9	0.6	0.3	1.2	41.4	-42.9	77.4	0.223
	HRV_POOL	2974	20	0.7	0.4	1.0	35.3	-35.8	68.5	0.208
	Placebo	1443	15	1.0	0.6	1.7	-	-	-	-
G12	HRV_2D	1496	20	1.3	0.8	2.1	37.8	-12.7	66.4	0.119
	HRV_3D	1478	14	0.9	0.5	1.6	55.9	14.6	78.3	0.010
	HRV_POOL	2974	34	1.1	0.8	1.6	46.8	10.5	68.3	0.011
	Placebo	1443	31	2.1	1.5	3.0	-	-	-	-
P4	HRV_2D	1496	27	1.8	1.2	2.6	40.8	2.3	64.8	0.031
	HRV_3D	1478	28	1.9	1.3	2.7	37.9	-2.1	62.8	0.056
	HRV_POOL	2974	55	1.8	1.4	2.4	39.3	7.7	59.9	0.017
	Placebo	1443	44	3.0	2.2	4.1	-	-	-	-
P6	HRV_2D	1496	20	1.3	0.8	2.1	35.7	-17.0	65.4	0.153
	HRV_3D	1478	13	0.9	0.5	1.5	57.7	16.4	79.7	0.008
	HRV_POOL	2974	33	1.1	0.8	1.6	46.6	9.4	68.4	0.014
	Placebo	1443	30	2.1	1.4	3.0	-	-	-	-
P8	HRV_2D	1496	49	3.3	2.4	4.3	53.7	34.2	67.7	<0.001
	HRV_3D	1478	33	2.2	1.5	3.1	68.4	52.8	79.3	<0.001
	HRV_POOL	2974	82	2.8	2.2	3.4	61.0	47.3	71.2	<0.001
	Placebo	1443	102	7.1	5.8	8.5	-	-	-	-
Non G1	HRV_2D	1496	62	4.1	3.2	5.3	38.3	14.3	55.9	0.002
	HRV_3D	1478	51	3.5	2.6	4.5	48.7	27.2	64.2	<0.001
	HRV_POOL	2974	113	3.8	3.1	4.6	43.5	25.1	57.3	<0.001
	Placebo	1443	97	6.7	5.5	8.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 102 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by Cox (ATP cohort for efficacy)

					Person-year rate			VE			
Event Type	Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any	HRV_POOL	2974	167	1813.93	0.0921	0.0791	0.1071	55.633	45.137	64.120	<0.0001
	Placebo	1443	174	833.09	0.2089	0.1800	0.2423	-	-	-	.

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 103 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by Cox (ATP cohort for efficacy, South Africa)

					Person-year rate			VE			
Event Type	Group	N	N	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any	HRV_POOL	1944	82	1195.35	0.0686	0.0552	0.0852	65.890	54.671	74.332	<0.0001
	Placebo	960	113	552.08	0.2047	0.1702	0.2461	-	-	-	.

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 104 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by Cox (ATP cohort for efficacy, Malawi)

					Person-year rate			VE			
Event Type	Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Any	HRV_POOL	1030	85	618.58	0.1374	0.1111	0.1700	36.928	12.365	54.606	0.0060
	Placebo	483	61	281.01	0.2171	0.1689	0.2790	-	-	-	.

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 105 Percentage of subjects reporting RVGE episode with score global_i equal to or greater than 11 on Vesikari scale excluding/including the 62 subjects with GE during vaccination

Excluding				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any	HRV_2D	1496	30	2.0	1.4	2.9	58.7	35.7	74.0	<0.0001
	HRV_3D	1478	26	1.8	1.2	2.6	63.7	42.4	77.8	<0.0001
	HRV_POOL	2974	56	1.9	1.4	2.4	61.2	44.0	73.2	<0.0001
	Placebo	1443	70	4.9	3.8	6.1	-	-	-	-
Including				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any	HRV_2D	1510	30	2.0	1.3	2.8	57.9	34.6	73.5	<0.0001
	HRV_3D	1487	26	1.7	1.1	2.6	63.0	41.2	77.4	<0.0001
	HRV_POOL	2997	56	1.9	1.4	2.4	60.4	43.0	72.7	<0.0001
	Placebo	1482	70	4.7	3.7	5.9	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 106 Percentage of subjects reporting RVGE episode excluding/including the 62 subjects with GE during vaccination excluded from ATP analyses with reasons for exclusion

Excluding				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any	HRV_2D	1496	93	6.2	5.0	7.6	48.4	33.3	60.4	<0.0001
	HRV_3D	1478	74	5.0	4.0	6.2	58.5	45.2	68.8	<0.0001
	HRV_POOL	2974	167	5.6	4.8	6.5	53.4	42.1	62.6	<0.0001
	Placebo	1443	174	12.1	10.4	13.9	-	-	-	-
Including				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
Any	HRV_2D	1510	94	6.2	5.1	7.6	47.0	31.5	59.2	<0.0001
	HRV_3D	1487	75	5.0	4.0	6.3	57.0	43.4	67.7	<0.0001
	HRV_POOL	2997	169	5.6	4.8	6.5	52.0	40.3	61.4	<0.0001
	Placebo	1482	174	11.7	10.1	13.5	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test
* = Two subjects had G8P[4] during vaccination.

Supplement 107 Percentage of subjects hospitalized and/or treated re-hydration therapy due to RV GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	78	5.2	4.1	6.5	51.8	36.3	63.7	<0.001
HRV_3D	1478	64	4.3	3.4	5.5	59.9	46.1	70.5	<0.001
HRV_POOL	2974	142	4.8	4.0	5.6	55.8	44.2	65.1	<0.001
Placebo	1443	156	10.8	9.3	12.5	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects hospitalized and/or treated with re-hydration therapy du to RV GE episode
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 108 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by South Africa cohorts (ATP cohort for efficacy)

				n/N			VE			
Cohorts in South Africa	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	553	13	2.4	1.3	4.0	64.9	32.5	82.9	<0.001
	HRV_3D	548	21	3.8	2.4	5.8	42.8	-0.3	68.2	0.042
	HRV_POOL	1101	34	3.1	2.1	4.3	53.9	24.5	71.9	0.001
	Placebo	552	37	6.7	4.8	9.1	-	-	-	-
2	HRV_2D	418	23	5.5	3.5	8.1	6.5	-73.0	49.5	0.881
	HRV_3D	425	12	2.8	1.5	4.9	52.0	0.2	78.1	0.040
	HRV_POOL	843	35	4.2	2.9	5.7	29.4	-24.0	59.2	0.200
	Placebo	408	24	5.9	3.8	8.6	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 109 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by country (ATP cohort for efficacy)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	525	98	18.7	15.4	22.3	22.9	-1.7	41.7	0.038
	HRV_3D	505	89	17.6	14.4	21.2	27.2	3.3	45.4	0.012
	HRV_POOL	1030	187	18.2	15.8	20.6	25.1	4.7	40.8	0.007
	Placebo	483	117	24.2	20.5	28.3	-	-	-	-
South Africa	HRV_2D	971	36	3.7	2.6	5.1	41.7	10.5	62.5	0.009
	HRV_3D	973	33	3.4	2.3	4.7	46.6	17.2	66.2	0.003
	HRV_POOL	1944	69	3.5	2.8	4.5	44.1	19.8	61.0	<0.001
	Placebo	960	61	6.4	4.9	8.1	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 110 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	540	36.1	33.7	38.6	6.7	-5.3	17.2	0.158
HRV_3D	1478	478	32.3	30.0	34.8	16.4	5.3	26.1	<0.001
HRV_POOL	2974	1018	34.2	32.5	36.0	11.5	1.7	20.2	0.004
Placebo	1443	558	38.7	36.1	41.2	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects reporting at least one GE episodes regardless of any cause in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test
Note: 2 sided Fisher exact test comparing 2 doses versus 3 doses=0.034

Supplement 111 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by country (ATP cohort for efficacy)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	525	244	46.5	42.1	50.8	9.8	-8.0	24.7	0.115
	HRV_3D	505	217	43.0	38.6	47.4	16.6	-0.4	30.8	0.007
	HRV_POOL	1030	461	44.8	41.7	47.9	13.2	-1.7	25.7	0.015
	Placebo	483	249	51.6	47.0	56.1	-	-	-	-
South Africa	HRV_2D	971	296	30.5	27.6	33.5	5.3	-11.4	19.5	0.433
	HRV_3D	973	261	26.8	24.1	29.7	16.7	1.4	29.6	0.011
	HRV_POOL	1944	557	28.7	26.7	30.7	11.0	-2.6	22.7	0.052
	Placebo	960	309	32.2	29.2	35.2	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects reporting at least one GE episodes regardless of any cause in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 112 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by cohorts in South Africa (ATP cohort for efficacy)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	553	172	31.1	27.3	35.1	12.8	-7.5	29.4	0.111
	HRV_3D	548	158	28.8	25.1	32.8	19.2	-0.1	34.9	0.017
	HRV_POOL	1101	330	30.0	27.3	32.8	16.0	-0.7	29.8	0.022
	Placebo	552	197	35.7	31.7	39.8	-	-	-	-
2	HRV_2D	418	124	29.7	25.3	34.3	-8.1	-40.8	17.0	0.489
	HRV_3D	425	103	24.2	20.2	28.6	11.7	-16.4	33.1	0.304
	HRV_POOL	843	227	26.9	24.0	30.1	1.9	-24.1	22.1	0.839
	Placebo	408	112	27.5	23.2	32.1	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects reporting at least one GE episodes regardless of any cause in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 113 Percentage of subjects hospitalized and/or treated re-hydration therapy due to GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	442	29.5	27.2	31.9	11.2	-1.3	22.1	0.032
HRV_3D	1478	381	25.8	23.6	28.1	22.5	11.2	32.4	<0.001
HRV_POOL	2974	823	27.7	26.1	29.3	16.8	6.7	25.8	<0.001
Placebo	1443	480	33.3	30.8	35.8	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects hospitalized and/or treated with re-hydration therapy du to GE episode
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 114 Percentage of subjects hospitalized due to GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	51	3.4	2.5	4.5	16.6	-23.4	43.8	0.382
HRV_3D	1478	37	2.5	1.8	3.4	38.8	6.1	60.5	0.017
HRV_POOL	2974	88	3.0	2.4	3.6	27.6	-2.4	48.5	0.060
Placebo	1443	59	4.1	3.1	5.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 115 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by status of anti rotavirus IgA antibody concentrations after dose 3 (ATP cohort for efficacy)

Anti-rotavirus IgA antibody status at visit 4				n/N			VE			
Status	Group	N	n	%	LL	UL	%	LL	UL	P-value
Negative	HRV_2D	510	53	10.4	7.9	13.4	17.3	-14.6	41.1	0.241
	HRV_3D	515	31	6.0	4.1	8.4	52.1	28.7	68.7	<0.001
	HRV_POOL	1025	84	8.2	6.6	10.0	34.8	13.5	51.1	0.001
	Placebo	1026	129	12.6	10.6	14.8	-	-	-	-
Positive	HRV_2D	895	35	3.9	2.7	5.4	57.5	27.5	74.9	<0.001
	HRV_3D	850	37	4.4	3.1	6.0	52.7	19.8	71.9	0.003
	HRV_POOL	1745	72	4.1	3.2	5.2	55.2	28.0	71.4	<0.001
	Placebo	304	28	9.2	6.2	13.0	-	-	-	-
Unknown	HRV_2D	91	5	5.5	1.8	12.4	63.5	-3.1	89.5	0.040
	HRV_3D	113	6	5.3	2.0	11.2	64.7	6.2	88.6	0.026
	HRV_POOL	204	11	5.4	2.7	9.4	64.2	18.9	84.8	0.006
	Placebo	113	17	15.0	9.0	23.0	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects reporting RVGE episode, by status of anti rotavirus IgA antibodies concentration at visit 4
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 116 Percentage of subjects reporting severe RV GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by status of anti rotavirus IgA antibody concentrations after dose 3 (ATP cohort for efficacy)

				n/N			VE			
Status	Group	N	n	%	LL	UL	%	LL	UL	P-value
Negative	HRV_2D	510	18	3.5	2.1	5.5	24.6	-32.1	58.7	0.350
	HRV_3D	515	11	2.1	1.1	3.8	54.3	10.8	78.6	0.016
	HRV_POOL	1025	29	2.8	1.9	4.0	39.5	2.1	63.2	0.036
	Placebo	1026	48	4.7	3.5	6.2	-	-	-	-
Positive	HRV_2D	895	9	1.0	0.5	1.9	78.2	45.8	91.7	<0.001
	HRV_3D	850	15	1.8	1.0	2.9	61.7	14.3	82.8	0.010
	HRV_POOL	1745	24	1.4	0.9	2.0	70.1	37.6	85.2	<0.001
	Placebo	304	14	4.6	2.5	7.6	-	-	-	-
Unknown	HRV_2D	91	3	3.3	0.7	9.3	53.4	-94.0	92.0	0.352
	HRV_3D	113	0	0.0	0.0	3.2	100.0	41.4	100.0	0.007
	HRV_POOL	204	3	1.5	0.3	4.2	79.2	13.5	96.5	0.020
	Placebo	113	8	7.1	3.1	13.5	-	-	-	-

N = number of subjects included in each group
n (%) = number (percentage)s of subjects reporting severe RVGE episode, by status of anti rotavirus IgA antibodies concentration at visit 4
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 117 Percentage of subjects reporting severe (Clark score equal to or greater than 17) RV E episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 (ATP cohort for efficacy)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1496	6	0.4	0.1	0.9	47.4	-55.2	84.0	0.229
HRV_3D	1478	5	0.3	0.1	0.8	55.6	-38.5	87.9	0.138
HRV_POOL	2974	11	0.4	0.2	0.7	51.5	-23.4	80.9	0.108
Placebo	1443	11	0.8	0.4	1.4	-	-	-	-

n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 118 Percentage of subjects reporting severe (Clark score equal to or greater than 17) RV GE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by country (ATP cohort for efficacy)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	525	6	1.1	0.4	2.5	38.7	-92.9	82.0	0.438
	HRV_3D	505	5	1.0	0.3	2.3	46.9	-76.6	86.0	0.289
	HRV_POOL	1030	11	1.1	0.5	1.9	42.7	-56.5	78.4	0.230
	Placebo	483	9	1.9	0.9	3.5	-	-	-	-
South Africa	HRV_2D	971	0	0.0	0.0	0.4	100.0	-426.4	100.0	0.247
	HRV_3D	973	0	0.0	0.0	0.4	100.0	-425.3	100.0	0.247
	HRV_POOL	1944	0	0.0	0.0	0.2	100.0	-162.9	100.0	0.109
	Placebo	960	2	0.2	0.0	0.8	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 119 Percentage of subjects reporting severe (Clark score equal to or greater than 17) RVGE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by cohort of South Africa (ATP cohort for efficacy)

				n/N			VE			
South Africa Cohorts	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	553	0	0.0	0.0	0.7	100.0	-3792.9	100.0	0.500
	HRV_3D	548	0	0.0	0.0	0.7	100.0	-3828.5	100.0	1.000
	HRV_POOL	1101	0	0.0	0.0	0.3	100.0	-1855.3	100.0	0.334
	Placebo	552	1	0.2	0.0	1.0	-	-	-	-
2	HRV_2D	418	0	0.0	0.0	0.9	100.0	-3706.7	100.0	0.494
	HRV_3D	425	0	0.0	0.0	0.9	100.0	-3644.0	100.0	0.490
	HRV_POOL	843	0	0.0	0.0	0.4	100.0	-1787.5	100.0	0.326
	Placebo	408	1	0.2	0.0	1.4	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 120 Percentage of subjects reporting severe (Clark score equal to or greater than 17) RVGE episode and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 by ELISA (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1 WT	HRV_2D	1496	0	0.0	0.0	0.2	100.0	-413.6	100.0	0.241
	HRV_3D	1478	0	0.0	0.0	0.2	100.0	-419.8	100.0	0.244
	HRV_POOL	2974	0	0.0	0.0	0.1	100.0	-158.4	100.0	0.107
	Placebo	1443	2	0.1	0.0	0.5	-	-	-	-
G2	HRV_2D	1496	0	0.0	0.0	0.2	100.0	-413.6	100.0	0.241
	HRV_3D	1478	0	0.0	0.0	0.2	100.0	-419.8	100.0	0.244
	HRV_POOL	2974	0	0.0	0.0	0.1	100.0	-158.4	100.0	0.107
	Placebo	1443	2	0.1	0.0	0.5	-	-	-	-
G8	HRV_2D	1496	3	0.2	0.0	0.6	-44.7	-1632.3	83.4	1.000
	HRV_3D	1478	1	0.1	0.0	0.4	51.2	-837.7	99.2	0.620
	HRV_POOL	2974	4	0.1	0.0	0.3	3.0	-972.8	86.1	1.000
	Placebo	1443	2	0.1	0.0	0.5	-	-	-	-
G9	HRV_2D	1496	2	0.1	0.0	0.5	-92.9	-11281.4	90.0	1.000
	HRV_3D	1478	0	0.0	0.0	0.2	100.0	-3707.6	100.0	0.494
	HRV_POOL	2974	2	0.1	0.0	0.2	3.0	-5625.1	94.9	1.000
	Placebo	1443	1	0.1	0.0	0.4	-	-	-	-
G12	HRV_2D	1496	1	0.1	0.0	0.4	75.9	-143.7	99.5	0.210
	HRV_3D	1478	4	0.3	0.1	0.7	2.4	-424.2	81.8	1.000
	HRV_POOL	2974	5	0.2	0.1	0.4	39.3	-205.7	86.9	0.486
	Placebo	1443	4	0.3	0.1	0.7	-	-	-	-
P4	HRV_2D	1496	2	0.1	0.0	0.5	51.8	-236.5	95.6	0.445
	HRV_3D	1478	1	0.1	0.0	0.4	75.6	-146.6	99.5	0.213
	HRV_POOL	2974	3	0.1	0.0	0.3	63.6	-115.1	94.7	0.226
	Placebo	1443	4	0.3	0.1	0.7	-	-	-	-
P6	HRV_2D	1496	1	0.1	0.0	0.4	67.8	-300.4	99.4	0.366
	HRV_3D	1478	2	0.1	0.0	0.5	34.9	-468.2	94.6	0.684
	HRV_POOL	2974	3	0.1	0.0	0.3	51.5	-262.3	93.5	0.400
	Placebo	1443	3	0.2	0.0	0.6	-	-	-	-
P8	HRV_2D	1496	3	0.2	0.0	0.6	27.7	-327.6	89.4	0.722
	HRV_3D	1478	1	0.1	0.0	0.4	75.6	-146.6	99.5	0.213
	HRV_POOL	2974	4	0.1	0.0	0.3	51.5	-160.5	91.0	0.451
	Placebo	1443	4	0.3	0.1	0.7	-	-	-	-
NonG1	HRV_2D	1496	6	0.4	0.1	0.9	35.7	-102.3	81.2	0.446
	HRV_3D	1478	5	0.3	0.1	0.8	45.8	-80.2	85.7	0.295
	HRV_POOL	2974	11	0.4	0.2	0.7	40.7	-61.9	77.7	0.240
	Placebo	1443	9	0.6	0.3	1.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 121 Percentage of subjects reporting RVGE episode with score equal to or greater than 17 on Clark scale and efficacy of the vaccine from 2 weeks after dose 3 up to visit 6 (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
≥17	HRV_2D	1496	6	0.4	0.1	0.9	47.4	-55.2	84.0	0.229
	HRV_3D	1478	5	0.3	0.1	0.8	55.6	-38.5	87.9	0.138
	HRV_POOL	2974	11	0.4	0.2	0.7	51.5	-23.4	80.9	0.108
	Placebo	1443	11	0.8	0.4	1.4	-	-	-	-
≥18	HRV_2D	1496	4	0.3	0.1	0.7	44.9	-116.8	88.2	0.379
	HRV_3D	1478	3	0.2	0.0	0.6	58.2	-83.3	93.0	0.221
	HRV_POOL	2974	7	0.2	0.1	0.5	51.5	-62.1	85.5	0.251
	Placebo	1443	7	0.5	0.2	1.0	-	-	-	-
≥19	HRV_2D	1496	3	0.2	0.0	0.6	27.7	-327.6	89.4	0.722
	HRV_3D	1478	3	0.2	0.0	0.6	26.8	-332.8	89.3	0.723
	HRV_POOL	2974	6	0.2	0.1	0.4	27.2	-250.7	82.7	0.737
	Placebo	1443	4	0.3	0.1	0.7	-	-	-	-
≥20	HRV_2D	1496	3	0.2	0.0	0.6	3.5	-620.2	87.1	1.000
	HRV_3D	1478	1	0.1	0.0	0.4	67.5	-305.3	99.4	0.369
	HRV_POOL	2974	4	0.1	0.0	0.3	35.3	-341.6	89.1	0.690
	Placebo	1443	3	0.2	0.0	0.6	-	-	-	-
≥21	HRV_2D	1496	2	0.1	0.0	0.5	-92.9	-11281.4	90.0	1.000
	HRV_3D	1478	1	0.1	0.0	0.4	2.4	-7563.8	98.8	1.000
	HRV_POOL	2974	3	0.1	0.0	0.3	-45.6	-7541.6	88.3	1.000
	Placebo	1443	1	0.1	0.0	0.4	-	-	-	-
≥22	HRV_2D	1496	1	0.1	0.0	0.4	3.5	-7471.6	98.8	1.000
	HRV_3D	1478	0	0.0	0.0	0.2	100.0	-3707.6	100.0	0.494
	HRV_POOL	2974	1	0.0	0.0	0.2	51.5	-3708.7	99.4	0.547
	Placebo	1443	1	0.1	0.0	0.4	-	-	-	-
≥23	HRV_2D	1496	0	0.0	0.0	0.2	.	.	.	-
	HRV_3D	1478	0	0.0	0.0	0.2	.	.	.	-
	HRV_POOL	2974	0	0.0	0.0	0.1	.	.	.	-
	Placebo	1443	0	0.0	0.0	0.3	-	-	-	-
≥24	HRV_2D	1496	0	0.0	0.0	0.2	.	.	.	-
	HRV_3D	1478	0	0.0	0.0	0.2	.	.	.	-
	HRV_POOL	2974	0	0.0	0.0	0.1	.	.	.	-
	Placebo	1443	0	0.0	0.0	0.3	-	-	-	-

N = number of subjects included in each group
n (%)= number (percentage)s of subjects reporting at least one RV GE episode ≥17 on the Clark scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 122 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Event	Total number of episodes reported	Value or n	%	Value or n	%	Value or n	%	Value or n	%
GE	0	949	57.6	1006	60.9	1955	59.3	914	55.7
	1	432	26.2	431	26.1	863	26.2	455	27.7
	2	177	10.7	148	9.0	325	9.9	185	11.3
	3	65	3.9	50	3.0	115	3.5	56	3.4
	4	15	0.9	10	0.6	25	0.8	23	1.4
	5	7	0.4	4	0.2	11	0.3	5	0.3
	6	2	0.1	1	0.1	3	0.1	2	0.1
	7	0	0.0	1	0.1	1	0.0	1	0.1
	Any	698	42.4	645	39.1	1343	40.7	727	44.3
RVGE	0	1534	93.1	1564	94.7	3098	93.9	1428	87.0
	1	112	6.8	86	5.2	198	6.0	211	12.9
	2	1	0.1	1	0.1	2	0.1	2	0.1
	Any	113	6.9	87	5.3	200	6.1	213	13.0
Severe GE	0	1484	90.1	1501	90.9	2985	90.5	1416	86.3
	1	133	8.1	130	7.9	263	8.0	190	11.6
	2	23	1.4	16	1.0	39	1.2	28	1.7
	3	6	0.4	4	0.2	10	0.3	5	0.3
	4	0	0.0	0	0.0	0	0.0	2	0.1
	5	1	0.1	0	0.0	1	0.0	0	0.0
	Any	163	9.9	150	9.1	313	9.5	225	13.7
Severe RVGE	0	1610	97.8	1620	98.1	3230	97.9	1558	94.9
	1	37	2.2	31	1.9	68	2.1	83	5.1
	Any	37	2.2	31	1.9	68	2.1	83	5.1

N = number of subject included in each group, for considered efficacy follow-up period
n (%) = number (percentage) subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 123 Percentage of GE episodes with no available stool results from dose 1 of HRV vaccine or placebo up to VISIT 6 (Total vaccinated cohort)

Category	HRV_2D N=1033		HRV_3D N=914		HRV_POOL N=1947		Placebo N=1038	
	n	%	n	%	n	%	n	%
No stool results available	146	13.4	118	12.4	264	13.6	159	14.1
no stools collected	133	12.2	110	11.6	243	12.5	142	12.6
stools collected but no results available	13	1.2	8	0.8	21	1.1	17	1.5

N = number of gastroenteritis episodes reported
N (%) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 124 Percentages of GE episodes with missing information for the number of looser than normal stools per day reported from Dose 1 up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1088		HRV_3D N = 950		HRV_POOL N =2038		Placebo N =1129		Total N = 3167	
Maximum number of stool	n	%	n	%	n	%	n	%	n	%
Missing or <3	59	5.4	39	4.1	98	4.8	41	3.6	139	4.4

N = number of GE episodes reported
n (%) = number (percentage) of GE episodes reported with maximum number of looser than normal stool <3 or missing per day during the episodes

Supplement 125 Number of GE episodes reported from dose 1 up to Visit 6 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%	n	%	n	%
GE	Mild (1-6)	538	49.4	455	47.9	993	48.7	456	40.4
	Moderate (7-10)	326	30.0	310	32.6	636	31.2	391	34.6
	Severe (>10)	202	18.6	174	18.3	376	18.4	269	23.8
	Unknown	22	2.0	11	1.2	33	1.6	13	1.2
	Any	1066	98.0	939	98.8	2005	98.4	1116	98.8
RV GE	Mild (1-6)	36	31.6	22	25.0	58	28.7	40	18.6
	Moderate (7-10)	41	36.0	35	39.8	76	37.6	91	42.3
	Severe (>10)	37	32.5	31	35.2	68	33.7	83	38.6
	Unknown	0	0.0	0	0.0	0	0.0	1	0.5
	Any	114	100	88	100	202	100	214	99.5

n (%) = number (percentage) of specified event reported in each group by severity using the 20-point Vesikari scale among all specified event reported the considered efficacy period
Any= any specified symptom reported and scored >0 in Vesikari severity scale
Unknown= symptom reported with Vesikari score =0

Supplement 126 Number of GE episodes reported from Dose 1 up to Visit 6 by severity using the 24-point Clark scale (Total vaccinated cohort)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 24 point Clark scale	n	%	n	%	n	%	n	%
GE	Mild (1-8)	777	71.4	659	69.4	1436	70.5	745	66.0
	Moderate (9-16)	222	20.4	226	23.8	448	22.0	307	27.2
	Severe (>16)	36	3.3	29	3.1	65	3.2	40	3.5
	Unknown	53	4.9	36	3.8	89	4.4	37	3.3
	Any	1035	95.1	914	96.2	1949	95.6	1092	96.7
RV GE	Mild (1-8)	74	64.9	43	48.9	117	57.9	112	52.1
	Moderate (9-16)	34	29.8	38	43.2	72	35.6	87	40.5
	Severe (>16)	6	5.3	5	5.7	11	5.4	13	6.0
	Unknown	0	0.0	2	2.3	2	1.0	3	1.4
	Any	114	100	86	97.7	200	99.0	212	98.6

n (%) = number (percentage) of specified event reported in each group by severity using the 24-point Clark scale among all specified event reported the considered efficacy period
Any= any specified symptom reported and scored >0 in Clark severity scale
Unknown= symptom reported with Clark score =0

Supplement 127 Percentage of subjects with RV GE episodes from dose 1 up to Visit 6 by G serotype and p genotype (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Serotype	n	%	n	%	n	%	n	%
Any	113	6.9	87	5.3	200	6.1	213	13.0
G1 vaccine type	3	0.2	1	0.1	4	0.1	0	0.0
G1 wild type	34	2.1	24	1.5	58	1.8	89	5.4
G2	16	1.0	18	1.1	34	1.0	28	1.7
G3	7	0.4	1	0.1	8	0.2	11	0.7
G8	24	1.5	17	1.0	41	1.2	32	2.0
G9	12	0.7	10	0.6	22	0.7	16	1.0
GX	24	1.5	19	1.2	43	1.3	46	2.8
P4	37	2.2	31	1.9	68	2.1	57	3.5
P6	25	1.5	19	1.2	44	1.3	41	2.5
P8 vaccine type	3	0.2	1	0.1	4	0.1	0	0.0
P8 wild type	53	3.2	37	2.2	90	2.7	118	7.2

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 128 Percentage of subjects with severe RV GE episodes from Dose 1 up to Visit 6 by G serotype and P genotype (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Characteristics	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Any	37	2.2	31	1.9	68	2.1	83	5.1
G1 wild type	9	0.5	9	0.5	18	0.5	27	1.6
G2	2	0.1	2	0.1	4	0.1	7	0.4
G3	2	0.1	0	0.0	2	0.1	6	0.4
G8	11	0.7	7	0.4	18	0.5	18	1.1
G9	6	0.4	2	0.1	8	0.2	10	0.6
GX	8	0.5	11	0.7	19	0.6	20	1.2
P4	10	0.6	8	0.5	18	0.5	23	1.4
P6	7	0.4	9	0.5	16	0.5	18	1.1
P8 wild type	20	1.2	14	0.8	34	1.0	44	2.7

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one severe RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 129 Percentage of subjects who were fully vaccinated (at least 2 weeks after dose3) before beginning of RV season* in South Africa (Total vaccinated cohort)

		HRV_2D N = 982		HRV_3D N = 980		HRV_POOL N = 1962		Placebo N = 983		Total N = 2945	
Characteristics	Vaccinated before RV season?	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
South Africa cohort 1	No	261	46.6	269	48.6	530	47.6	263	47.0	793	47.4
	Yes	299	53.4	285	51.4	584	52.4	297	53.0	881	52.6
South Africa cohort 2	No	239	56.6	239	56.1	478	56.4	248	58.6	726	57.1
	Yes	183	43.4	187	43.9	370	43.6	175	41.4	545	42.9
South Africa	No	500	50.9	508	51.8	1008	51.4	511	52.0	1519	51.6
	Yes	482	49.1	472	48.2	954	48.6	472	48.0	1426	48.4

N = number of subjects included in each group
n (%) = number (percentage) of subjects in specified category
*Starting of RV season in South Africa is 1st of March

Supplement 130 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6, by G and P type (Total vaccinated cohort)

Serotype	HRV_2D N'=114		HRV_3D N'=88		HRV_POOL N'=202		Placebo N'=215	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	3	2.63	1	1.14	4	1.98	0	0.00
G1WT+G2+G3+P4+P8WT	1	0.88	0	0.00	1	0.50	0	0.00
G1WT+G2+P4	2	1.75	1	1.14	3	1.49	0	0.00
G1WT+G2+P4+P8WT	2	1.75	1	1.14	3	1.49	1	0.47
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	2	0.93
G1WT+G8+P8WT	0	0.00	0	0.00	0	0.00	1	0.47
G1WT+P4	0	0.00	0	0.00	0	0.00	1	0.47
G1WT+P6	0	0.00	0	0.00	0	0.00	2	0.93
G1WT+P8WT	29	25.44	22	25.00	51	25.25	83	38.60
G2+G8+P4	0	0.00	1	1.14	1	0.50	1	0.47
G2+P4	11	9.65	14	15.91	25	12.38	26	12.09
G2+P4+P8WT	0	0.00	1	1.14	1	0.50	0	0.00
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	1.40
G3+P8WT	6	5.26	1	1.14	7	3.47	6	2.79
G8+P4	20	17.54	13	14.77	33	16.34	27	12.56
G8+P4+P6	1	0.88	0	0.00	1	0.50	0	0.00
G8+P6	1	0.88	1	1.14	2	0.99	0	0.00
G8+P8WT	2	1.75	2	2.27	4	1.98	0	0.00
G9+P6	1	0.88	1	1.14	2	0.99	0	0.00
G9+P8WT	11	9.65	9	10.23	20	9.90	16	7.44
GX	0	0.00	1	1.14	1	0.50	0	0.00
GX+P4	0	0.00	0	0.00	0	0.00	1	0.47
GX+P6	22	19.30	17	19.32	39	19.31	38	17.67
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	0.47
GX+P8WT	2	1.75	1	1.14	3	1.49	6	2.79
Unknown	0	0.00	1	1.14	1	0.50	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to VISIT 6
GX=G12 Sero Type

Supplement 131 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6, by G and P type (Total vaccinated cohort, South Africa cohort 1)

Serotype	HRV_2D N'=29		HRV_3D N'=23		HRV_POOL N'=52		Placebo N'=79	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	3.45	1	4.35	2	3.85	0	0.00
G1WT+G2+G3+P4+P8WT	1	3.45	0	0.00	1	1.92	0	0.00
G1WT+G2+P4	0	0.00	1	4.35	1	1.92	0	0.00
G1WT+G2+P4+P8WT	1	3.45	1	4.35	2	3.85	0	0.00
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	2	2.53
G1WT+P6	0	0.00	0	0.00	0	0.00	1	1.27
G1WT+P8WT	15	51.72	12	52.17	27	51.92	53	67.09
G2+G8+P4	0	0.00	0	0.00	0	0.00	1	1.27
G2+P4	1	3.45	1	4.35	2	3.85	1	1.27
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	3.80
G3+P8WT	6	20.69	1	4.35	7	13.46	6	7.59
G8+P4	0	0.00	2	8.70	2	3.85	5	6.33
G9+P6	1	3.45	1	4.35	2	3.85	0	0.00
G9+P8WT	0	0.00	1	4.35	1	1.92	0	0.00
GX+P6	3	10.34	2	8.70	5	9.62	7	8.86

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to VISIT 6
GX=G12 Sero Type

Supplement 132 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to Visit 6, by G and P type (Total vaccinated cohort, South Africa cohort 2)

Serotype	HRV_2D N'=25		HRV_3D N'=14		HRV_POOL N'=39		Placebo N'=50	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	4.00	0	0.00	1	2.56	0	0.00
G1WT+G2+P4	2	8.00	0	0.00	2	5.13	0	0.00
G1WT+G2+P4+P8 WT	1	4.00	0	0.00	1	2.56	1	2.00
G1WT+P4	0	0.00	0	0.00	0	0.00	1	2.00
G1WT+P8WT	11	44.00	4	28.57	15	38.46	22	44.00
G2+P4	8	32.00	9	64.29	17	43.59	22	44.00
GX+P6	2	8.00	1	7.14	3	7.69	4	8.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to Visit 6
GX=G12 Sero Type

Supplement 133 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6, by G and P type (Total vaccinated cohort, South Africa cohort)

Serotype	HRV_2D N'=54		HRV_3D N'=37		HRV_POOL N'=91		Placebo N'=129	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	2	3.70	1	2.70	3	3.30	0	0.00
G1WT+G2+G3+P4+P8WT	1	1.85	0	0.00	1	1.10	0	0.00
G1WT+G2+P4	2	3.70	1	2.70	3	3.30	0	0.00
G1WT+G2+P4+P8WT	2	3.70	1	2.70	3	3.30	1	0.78
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	2	1.55
G1WT+P4	0	0.00	0	0.00	0	0.00	1	0.78
G1WT+P6	0	0.00	0	0.00	0	0.00	1	0.78
G1WT+P8WT	26	48.15	16	43.24	42	46.15	75	58.14
G2+G8+P4	0	0.00	0	0.00	0	0.00	1	0.78
G2+P4	9	16.67	10	27.03	19	20.88	23	17.83
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	2.33
G3+P8WT	6	11.11	1	2.70	7	7.69	6	4.65
G8+P4	0	0.00	2	5.41	2	2.20	5	3.88
G9+P6	1	1.85	1	2.70	2	2.20	0	0.00
G9+P8WT	0	0.00	1	2.70	1	1.10	0	0.00
GX+P6	5	9.26	3	8.11	8	8.79	11	8.53

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to VISIT 6
GX=G12 Sero Type

Supplement 134 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to Visit 6, by G and P type (Total vaccinated cohort, Malawi cohort)

Serotype	HRV_2D N'=60		HRV_3D N'=51		HRV_POOL N'=111		Placebo N'=86	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	1.67	0	0.00	1	0.90	0	0.00
G1WT+G8+P8WT	0	0.00	0	0.00	0	0.00	1	1.16
G1WT+P6	0	0.00	0	0.00	0	0.00	1	1.16
G1WT+P8WT	3	5.00	6	11.76	9	8.11	8	9.30
G2+G8+P4	0	0.00	1	1.96	1	0.90	0	0.00
G2+P4	2	3.33	4	7.84	6	5.41	3	3.49
G2+P4+P8WT	0	0.00	1	1.96	1	0.90	0	0.00
G8+P4	20	33.33	11	21.57	31	27.93	22	25.58
G8+P4+P6	1	1.67	0	0.00	1	0.90	0	0.00
G8+P6	1	1.67	1	1.96	2	1.80	0	0.00
G8+P8WT	2	3.33	2	3.92	4	3.60	0	0.00
G9+P8WT	11	18.33	8	15.69	19	17.12	16	18.60
GX	0	0.00	1	1.96	1	0.90	0	0.00
GX+P4	0	0.00	0	0.00	0	0.00	1	1.16
GX+P6	17	28.33	14	27.45	31	27.93	27	31.40
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	1.16
GX+P8WT	2	3.33	1	1.96	3	2.70	6	6.98
Unknown	0	0.00	1	1.96	1	0.90	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to Visit 6
GX=G12 Sero Type

Supplement 135 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to Visit 6, by G and P type (Total vaccinated cohort)

Serotype	HRV_2D N'=37		HRV_3D N'=31		HRV_POOL N'=68		Placebo N'=83	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	2.70	0	0.00	1	1.47	0	0.00
G1WT+G2+P4+P8WT	0	0.00	0	0.00	0	0.00	1	1.20
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	1	1.20
G1WT+P4	0	0.00	0	0.00	0	0.00	1	1.20
G1WT+P6	0	0.00	0	0.00	0	0.00	1	1.20
G1WT+P8WT	8	21.62	9	29.03	17	25.00	23	27.71
G2+P4	1	2.70	1	3.23	2	2.94	6	7.23
G2+P4+P8WT	0	0.00	1	3.23	1	1.47	0	0.00
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	3.61
G3+P8WT	2	5.41	0	0.00	2	2.94	2	2.41
G8+P4	8	21.62	6	19.35	14	20.59	15	18.07
G8+P6	1	2.70	0	0.00	1	1.47	0	0.00
G8+P8WT	2	5.41	1	3.23	3	4.41	0	0.00
G9+P8WT	6	16.22	2	6.45	8	11.76	10	12.05
GX	0	0.00	1	3.23	1	1.47	0	0.00
GX+P6	6	16.22	9	29.03	15	22.06	16	19.28
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	1.20
GX+P8WT	2	5.41	1	3.23	3	4.41	3	3.61

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to Visit 6
GX=G12 Sero Type

Supplement 136 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to Visit 6, by G and P type (Total vaccinated cohort, South Africa cohort 1)

Serotype	HRV_2D N'=4		HRV_3D N'=5		HRV_POOL N'=9		Placebo N'=24	
	n	%	n	%	n	%	n	%
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	1	4.17
G1WT+P8WT	2	50.00	4	80.00	6	66.67	14	58.33
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	12.50
G3+P8WT	2	50.00	0	0.00	2	22.22	2	8.33
G8+P4	0	0.00	0	0.00	0	0.00	2	8.33
GX+P6	0	0.00	1	20.00	1	11.11	2	8.33

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to Visit 6
GX=G12 Sero Type

Supplement 137 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6, by G and P type (Total vaccinated cohort, South Africa cohort 2)

Serotype	HRV_2D N'=6		HRV_3D N'=1		HRV_POOL N'=7		Placebo N'=12	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	16.67	0	0.00	1	14.29	0	0.00
G1WT+G2+P4+P8 WT	0	0.00	0	0.00	0	0.00	1	8.33
G1WT+P4	0	0.00	0	0.00	0	0.00	1	8.33
G1WT+P8WT	4	66.67	1	100.0	5	71.43	5	41.67
G2+P4	1	16.67	0	0.00	1	14.29	5	41.67

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to Visit 6

Supplement 138 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6, by G and P type (Total vaccinated cohort, South Africa cohort)

Serotype	HRV_2D N'=10		HRV_3D N'=6		HRV_POOL N'=16		Placebo N'=36	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	10.00	0	0.00	1	6.25	0	0.00
G1WT+G2+P4+P8WT	0	0.00	0	0.00	0	0.00	1	2.78
G1WT+G3+P8WT	0	0.00	0	0.00	0	0.00	1	2.78
G1WT+P4	0	0.00	0	0.00	0	0.00	1	2.78
G1WT+P8WT	6	60.00	5	83.33	11	68.75	19	52.78
G2+P4	1	10.00	0	0.00	1	6.25	5	13.89
G3+G8+P8WT	0	0.00	0	0.00	0	0.00	3	8.33
G3+P8WT	2	20.00	0	0.00	2	12.50	2	5.56
G8+P4	0	0.00	0	0.00	0	0.00	2	5.56
GX+P6	0	0.00	1	16.67	1	6.25	2	5.56

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to VISIT 6
GX=G12 Sero Type

Supplement 139 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6, by G and P type (Total vaccinated cohort, Malawi)

Serotype	HRV_2D N'=27		HRV_3D N'=25		HRV_POOL N'=52		Placebo N'=47	
	n	%	n	%	n	%	n	%
G1WT+P6	0	0.00	0	0.00	0	0.00	1	2.13
G1WT+P8WT	2	7.41	4	16.00	6	11.54	4	8.51
G2+P4	0	0.00	1	4.00	1	1.92	1	2.13
G2+P4+P8WT	0	0.00	1	4.00	1	1.92	0	0.00
G8+P4	8	29.63	6	24.00	14	26.92	13	27.66
G8+P6	1	3.70	0	0.00	1	1.92	0	0.00
G8+P8WT	2	7.41	1	4.00	3	5.77	0	0.00
G9+P8WT	6	22.22	2	8.00	8	15.38	10	21.28
GX	0	0.00	1	4.00	1	1.92	0	0.00
GX+P6	6	22.22	8	32.00	14	26.92	14	29.79
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	2.13
GX+P8WT	2	7.41	1	4.00	3	5.77	3	6.38

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to VISIT 6
GX=G12 Sero Type

Supplement 140 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to visit 6 (Total vaccinated cohort)

		HRV_2D N = 114		HRV_3D N = 88		HRV_POOL N = 202		Placebo N = 215	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	8.9	-	9.2	-	9.0	-	9.5	-
	SD	3.9	-	3.7	-	3.8	-	3.5	-
	Median	9.0	-	9.0	-	9.0	-	10.0	-
	Minimum	2.0	-	1.0	-	1.0	-	0.0	-
	Maximum	19.0	-	19.0	-	19.0	-	19.0	-
Duration of looser than normal stools (days)	0 day	0	0.0	3	3.4	3	1.5	4	1.9
	1 to 4 days	79	69.3	68	77.3	147	72.8	155	72.1
	5	8	7.0	10	11.4	18	8.9	20	9.3
	more than 5 days	27	23.7	7	8.0	34	16.8	36	16.7
Maximum number of looser than normal stools/day	0	0	0.0	3	3.4	3	1.5	4	1.9
	1 to 3	17	14.9	13	14.8	30	14.9	23	10.7
	4 to 5	43	37.7	29	33.0	72	35.6	100	46.5
	more than 5	54	47.4	43	48.9	97	48.0	88	40.9
Duration of vomiting-days	0 day	42	36.8	23	26.1	65	32.2	51	23.7
	1 day	27	23.7	24	27.3	51	25.2	60	27.9
	2 days	20	17.5	21	23.9	41	20.3	37	17.2
	more than 2 days	25	21.9	20	22.7	45	22.3	67	31.2
Max number of episodes of vomiting/day	0	42	36.8	23	26.1	65	32.2	51	23.7
	1	8	7.0	4	4.5	12	5.9	14	6.5
	2 to 4	38	33.3	35	39.8	73	36.1	100	46.5
	more than 4	26	22.8	26	29.5	52	25.7	50	23.3
Maximum fever reported/day	less than 37.1°C	25	21.9	18	20.5	43	21.3	45	20.9
	37.1 to 38.4°C	75	65.8	47	53.4	122	60.4	123	57.2
	38.5 to 38.9°C	7	6.1	15	17.0	22	10.9	24	11.2
	more than 38.9°C	7	6.1	8	9.1	15	7.4	23	10.7
Treatment	none	19	16.7	12	13.6	31	15.3	25	11.6
	rehydration	82	71.9	69	78.4	151	74.8	171	79.5
	hospitalization	13	11.4	7	8.0	20	9.9	19	8.8
Dehydration	none	89	78.1	70	79.5	159	78.7	166	77.2
	1 to 5%	21	18.4	15	17.0	36	17.8	41	19.1
	more than 5 %	4	3.5	3	3.4	7	3.5	8	3.7

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 141 Characteristics of the GE episodes (based on Vesikari scale) reported from Dose 1 up to visit 6 (Total vaccinated cohort)

		HRV_2D N = 2037		HRV_3D N = 1956		HRV_POOL N = 3993		Placebo N = 2043	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Vesikari severity score	Mean	7.1	-	7.2	-	7.2	-	7.8	-
	SD	3.8	-	3.8	-	3.8	-	3.9	-
	Median	6.0	-	7.0	-	6.0	-	7.0	-
	Minimum	0.0	-	0.0	-	0.0	-	0.0	-
	Maximum	20.0	-	19.0	-	20.0	-	20.0	-
Duration of looser than normal stools (days)	0 day	59	2.9	38	1.9	97	2.4	40	2.0
	1 to 4 days	734	36.0	649	33.2	1383	34.6	766	37.5
	5	74	3.6	83	4.2	157	3.9	104	5.1
	more than 5 days	221	10.8	180	9.2	401	10.0	219	10.7
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7
Maximum number of looser than normal stools/day	0	59	2.9	38	1.9	97	2.4	40	2.0
	1 to 3	197	9.7	159	8.1	356	8.9	188	9.2
	4 to 5	448	22.0	418	21.4	866	21.7	474	23.2
	more than 5	384	18.9	335	17.1	719	18.0	427	20.9
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7
Duration of vomiting-days	0 day	670	32.9	553	28.3	1223	30.6	578	28.3
	1 day	186	9.1	171	8.7	357	8.9	224	11.0
	2 days	100	4.9	98	5.0	198	5.0	128	6.3
	more than 2 days	132	6.5	128	6.5	260	6.5	199	9.7
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7
Max number of episodes of vomiting/day	0	670	32.9	553	28.3	1223	30.6	578	28.3
	1	85	4.2	76	3.9	161	4.0	86	4.2
	2 to 4	225	11.0	225	11.5	450	11.3	327	16.0
	more than 4	108	5.3	96	4.9	204	5.1	138	6.8
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7
Maximum fever reported/day	less than 37.1°C	360	17.7	297	15.2	657	16.5	321	15.7
	37.1 to 38.4°C	558	27.4	510	26.1	1068	26.7	609	29.8
	38.5 to 38.9°C	56	2.7	57	2.9	113	2.8	97	4.7
	more than 38.9°C	114	5.6	86	4.4	200	5.0	102	5.0
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7
Treatment	none	272	13.4	224	11.5	496	12.4	241	11.8
	rehydration	741	36.4	675	34.5	1416	35.5	805	39.4
	hospitalization	75	3.7	51	2.6	126	3.2	83	4.1
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7
Dehydration	none	918	45.1	811	41.5	1729	43.3	921	45.1
	1 to 5%	139	6.8	124	6.3	263	6.6	166	8.1
	more than 5 %	31	1.5	15	0.8	46	1.2	42	2.1
	Missing	949	46.6	1006	51.4	1955	49.0	914	44.7

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 142 Duration (in years) of efficacy follow-up period - from Dose 1 up to Visit 6 - (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 1647	HRV_3D N = 1651	HRV_POOL N = 3298	Placebo N = 1641
Parameters or Categories	Value or n	Value or n	Value or n	Value or n
Sum	1331	1308	2639	1303
Mean	0.81	0.79	0.80	0.79
Minimum	0.00	0.00	0.00	0.00
Q1	0.85	0.85	0.85	0.85
Median	0.88	0.88	0.88	0.88
Q3	0.89	0.89	0.89	0.89
Maximum	1.52	2.26	2.26	1.47

N = number of subject included in each group
Sum = sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 143 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	113	6.9	5.7	8.2	47.1	33.3	58.3	<0.001
HRV_3D	1651	87	5.3	4.2	6.5	59.4	47.7	68.7	<0.001
HRV_POOL	3298	200	6.1	5.3	6.9	53.3	43.1	61.7	<0.001
Placebo	1641	213	13.0	11.4	14.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 144 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	59	10.0	7.7	12.7	30.5	1.9	51.0	0.026
	HRV_3D	592	50	8.4	6.3	11.0	41.3	15.8	59.4	0.001
	HRV_POOL	1182	109	9.2	7.6	11.0	35.9	13.8	52.2	0.001
	Placebo	591	85	14.4	11.7	17.5	-	-	-	-
South Africa	HRV_2D	1057	54	5.1	3.9	6.6	58.1	42.0	70.1	<0.001
	HRV_3D	1059	37	3.5	2.5	4.8	71.3	58.4	80.7	<0.001
	HRV_POOL	2116	91	4.3	3.5	5.3	64.7	53.5	73.3	<0.001
	Placebo	1050	128	12.2	10.3	14.3	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 145 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by South Africa cohort (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	29	4.8	3.2	6.8	63.1	42.9	76.8	<0.001
	HRV_3D	612	23	3.8	2.4	5.6	70.9	53.1	82.5	<0.001
	HRV_POOL	1222	52	4.3	3.2	5.5	67.0	52.5	77.2	<0.001
	Placebo	605	78	12.9	10.3	15.8	-	-	-	-
2	HRV_2D	447	25	5.6	3.7	8.1	50.2	18.0	70.5	0.002
	HRV_3D	447	14	3.1	1.7	5.2	72.1	48.8	85.8	<0.001
	HRV_POOL	894	39	4.4	3.1	5.9	61.2	39.8	75.1	<0.001
	Placebo	445	50	11.2	8.5	14.5	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 146 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV serotype (ATP cohort for efficacy)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV_2D	1647	34	2.1	1.4	2.9	61.9	42.9	75.1	<0.001
	HRV_3D	1651	24	1.5	0.9	2.2	73.2	57.5	83.7	<0.001
	HRV_POOL	3298	58	1.8	1.3	2.3	67.6	54.4	77.1	<0.001
	Placebo	1641	89	5.4	4.4	6.6	-	-	-	-
G2	HRV_2D	1647	16	1.0	0.6	1.6	43.1	-8.9	71.2	0.070
	HRV_3D	1651	18	1.1	0.6	1.7	36.1	-19.7	66.7	0.140
	HRV_POOL	3298	34	1.0	0.7	1.4	39.6	-3.4	64.4	0.057
	Placebo	1641	28	1.7	1.1	2.5	-	-	-	-
G3	HRV_2D	1647	7	0.4	0.2	0.9	36.6	-79.1	79.2	0.357
	HRV_3D	1651	1	0.1	0.0	0.3	91.0	37.8	99.8	0.003
	HRV_POOL	3298	8	0.2	0.1	0.5	63.8	1.2	87.4	0.028
	Placebo	1641	11	0.7	0.3	1.2	-	-	-	-
G8	HRV_2D	1647	24	1.5	0.9	2.2	25.3	-30.9	57.9	0.284
	HRV_3D	1651	17	1.0	0.6	1.6	47.2	2.0	72.5	0.031
	HRV_POOL	3298	41	1.2	0.9	1.7	36.2	-4.6	60.8	0.060
	Placebo	1641	32	2.0	1.3	2.7	-	-	-	-
G9	HRV_2D	1647	12	0.7	0.4	1.3	25.3	-68.4	67.7	0.456
	HRV_3D	1651	10	0.6	0.3	1.1	37.9	-45.6	74.8	0.245
	HRV_POOL	3298	22	0.7	0.4	1.0	31.6	-39.4	65.7	0.299
	Placebo	1641	16	1.0	0.6	1.6	-	-	-	-
G12	HRV_2D	1647	24	1.5	0.9	2.2	48.0	13.1	69.7	0.008
	HRV_3D	1651	19	1.2	0.7	1.8	58.9	28.5	77.3	<0.001
	HRV_POOL	3298	43	1.3	0.9	1.8	53.5	27.9	70.0	<0.001
	Placebo	1641	46	2.8	2.1	3.7	-	-	-	-
P4	HRV_2D	1647	37	2.2	1.6	3.1	35.3	0.5	58.4	0.037
	HRV_3D	1651	31	1.9	1.3	2.7	45.9	14.8	66.3	0.005
	HRV_POOL	3298	68	2.1	1.6	2.6	40.6	14.1	58.9	0.004
	Placebo	1641	57	3.5	2.6	4.5	-	-	-	-
P6	HRV_2D	1647	25	1.5	1.0	2.2	39.2	-2.3	64.6	0.047
	HRV_3D	1651	19	1.2	0.7	1.8	53.9	18.8	74.8	0.004
	HRV_POOL	3298	44	1.3	1.0	1.8	46.6	16.2	65.9	0.005
	Placebo	1641	41	2.5	1.8	3.4	-	-	-	-
P8	HRV_2D	1647	56	3.4	2.6	4.4	52.7	34.5	66.2	<0.001
	HRV_3D	1651	38	2.3	1.6	3.1	68.0	53.5	78.4	<0.001
	HRV_POOL	3298	94	2.9	2.3	3.5	60.4	47.6	70.1	<0.001
	Placebo	1641	118	7.2	6.0	8.5	-	-	-	-
Non G1	HRV_2D	1647	76	4.6	3.7	5.7	39.4	18.8	55.1	<0.001
	HRV_3D	1651	62	3.8	2.9	4.8	50.7	32.6	64.2	<0.001
	HRV_POOL	3298	138	4.2	3.5	4.9	45.1	29.5	57.2	<0.001
	Placebo	1641	125	7.6	6.4	9.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 147 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	37	2.2	1.6	3.1	55.6	33.8	70.7	<0.001
HRV_3D	1651	31	1.9	1.3	2.7	62.9	43.3	76.3	<0.001
HRV_POOL	3298	68	2.1	1.6	2.6	59.2	43.1	70.9	<0.001
Placebo	1641	83	5.1	4.0	6.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 148 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by South Africa cohorts (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	4	0.7	0.2	1.7	83.5	51.9	95.8	<0.001
	HRV_3D	612	5	0.8	0.3	1.9	79.4	44.9	93.9	<0.001
	HRV_POOL	1222	9	0.7	0.3	1.4	81.4	58.6	92.4	<0.001
	Placebo	605	24	4.0	2.6	5.8	-	-	-	-
2	HRV_2D	447	6	1.3	0.5	2.9	50.2	-43.3	84.7	0.162
	HRV_3D	447	1	0.2	0.0	1.2	91.7	43.9	99.8	0.002
	HRV_POOL	894	7	0.8	0.3	1.6	71.0	20.0	90.3	0.012
	Placebo	445	12	2.7	1.4	4.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 149 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	27	4.6	3.0	6.6	42.5	5.7	65.5	0.022
	HRV_3D	592	25	4.2	2.8	6.2	46.9	12.0	68.7	0.007
	HRV_POOL	1182	52	4.4	3.3	5.7	44.7	16.1	63.4	0.003
	Placebo	591	47	8.0	5.9	10.4	-	-	-	-
South Africa	HRV_2D	1057	10	0.9	0.5	1.7	72.4	43.2	87.8	<0.001
	HRV_3D	1059	6	0.6	0.2	1.2	83.5	60.4	94.3	<0.001
	HRV_POOL	2116	16	0.8	0.4	1.2	77.9	59.2	88.6	<0.001
	Placebo	1050	36	3.4	2.4	4.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 150 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 for the subset of subjects who were fully vaccinate before or after start of RV season (Total vaccinated cohort)

				n/N			VE			
	Group	N	n	%	LL	UL	%	LL	UL	P-value
Vaccination completed after RV season start	HRV_2D	500	5	1.0	0.3	2.3	68.1	8.8	90.8	0.025
	HRV_3D	508	3	0.6	0.1	1.7	81.1	34.1	96.5	0.004
	HRV_POOL	1008	8	0.8	0.3	1.6	74.7	37.2	90.6	0.002
	Placebo	511	16	3.1	1.8	5.0	-	-	-	-
Vaccination completed before RV season start	HRV_2D	482	5	1.0	0.3	2.4	75.5	32.8	92.8	0.002
	HRV_3D	472	3	0.6	0.1	1.8	85.0	49.4	97.1	<0.001
	HRV_POOL	954	8	0.8	0.4	1.6	80.2	53.1	92.5	<0.001
	Placebo	472	20	4.2	2.6	6.5	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test
RV season starts at 1st of March in South Africa

Supplement 151 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

				n/N			VE			
Event Type	Group	N	n	%	LL	UL	%	LL	UL	P-value
G1WT	HRV_2D	1647	9	0.5	0.3	1.0	66.8	27.2	86.3	0.002
	HRV_3D	1651	9	0.5	0.2	1.0	66.9	27.4	86.3	0.002
	HRV_POOL	3298	18	0.5	0.3	0.9	66.8	37.5	82.8	<0.001
	Placebo	1641	27	1.6	1.1	2.4	-	-	-	-
G2	HRV_2D	1647	2	0.1	0.0	0.4	71.5	-49.5	97.1	0.108
	HRV_3D	1651	2	0.1	0.0	0.4	71.6	-49.1	97.1	0.108
	HRV_POOL	3298	4	0.1	0.0	0.3	71.6	-11.8	93.9	0.049
	Placebo	1641	7	0.4	0.2	0.9	-	-	-	-
G3	HRV_2D	1647	2	0.1	0.0	0.4	66.8	-85.7	96.7	0.178
	HRV_3D	1651	0	0.0	0.0	0.2	100.0	15.6	100.0	0.015
	HRV_POOL	3298	2	0.1	0.0	0.2	83.4	7.2	98.4	0.019
	Placebo	1641	6	0.4	0.1	0.8	-	-	-	-
G8	HRV_2D	1647	11	0.7	0.3	1.2	39.1	-36.1	74.0	0.198
	HRV_3D	1651	7	0.4	0.2	0.9	61.3	3.0	86.4	0.028
	HRV_POOL	3298	18	0.5	0.3	0.9	50.2	-1.4	75.6	0.049
	Placebo	1641	18	1.1	0.7	1.7	-	-	-	-
G9	HRV_2D	1647	6	0.4	0.1	0.8	40.2	-81.5	82.1	0.330
	HRV_3D	1651	2	0.1	0.0	0.4	80.1	6.7	97.9	0.022
	HRV_POOL	3298	8	0.2	0.1	0.5	60.2	-12.0	86.3	0.075
	Placebo	1641	10	0.6	0.3	1.1	-	-	-	-
G12	HRV_2D	1647	8	0.5	0.2	1.0	60.1	5.5	84.8	0.023
	HRV_3D	1651	11	0.7	0.3	1.2	45.3	-19.7	76.3	0.108
	HRV_POOL	3298	19	0.6	0.3	0.9	52.7	6.7	76.1	0.025
	Placebo	1641	20	1.2	0.7	1.9	-	-	-	-
P4	HRV_2D	1647	10	0.6	0.3	1.1	56.7	5.4	81.6	0.023
	HRV_3D	1651	8	0.5	0.2	1.0	65.4	19.9	86.6	0.007
	HRV_POOL	3298	18	0.5	0.3	0.9	61.1	24.6	80.2	0.003
	Placebo	1641	23	1.4	0.9	2.1	-	-	-	-
P6	HRV_2D	1647	7	0.4	0.2	0.9	61.3	2.8	86.3	0.028
	HRV_3D	1651	9	0.5	0.2	1.0	50.3	-16.5	80.3	0.085
	HRV_POOL	3298	16	0.5	0.3	0.8	55.8	8.1	78.9	0.018
	Placebo	1641	18	1.1	0.7	1.7	-	-	-	-
P8	HRV_2D	1647	20	1.2	0.7	1.9	54.7	21.5	74.7	0.002
	HRV_3D	1651	14	0.8	0.5	1.4	68.4	41.2	84.0	<0.001
	HRV_POOL	3298	34	1.0	0.7	1.4	61.6	38.5	76.2	<0.001
	Placebo	1641	44	2.7	2.0	3.6	-	-	-	-
NonG1	HRV_2D	1647	28	1.7	1.1	2.4	50.2	20.2	69.5	0.002
	HRV_3D	1651	22	1.3	0.8	2.0	61.0	35.0	77.3	<0.001
	HRV_POOL	3298	50	1.5	1.1	2.0	55.6	33.8	70.3	<0.001
	Placebo	1641	56	3.4	2.6	4.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 152 Percentage of subjects reporting severe (Clark score >16) RV GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	6	0.4	0.1	0.8	54.0	-29.7	85.7	0.114
HRV_3D	1651	5	0.3	0.1	0.7	61.8	-14.3	89.3	0.062
HRV_POOL	3298	11	0.3	0.2	0.6	57.9	-1.8	82.9	0.048
Placebo	1641	13	0.8	0.4	1.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 153 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	163	9.9	8.5	11.4	27.8	11.3	41.4	<0.001
HRV_3D	1651	150	9.1	7.7	10.6	33.7	18.2	46.5	<0.001
HRV_POOL	3298	313	9.5	8.5	10.5	30.8	17.5	41.9	<0.001
Placebo	1641	225	13.7	12.1	15.5	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 154 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	114	19.3	16.2	22.7	17.8	-6.0	36.4	0.089
	HRV_3D	592	107	18.1	15.1	21.4	23.2	0.4	40.8	0.022
	HRV_POOL	1182	221	18.7	16.5	21.0	20.5	1.0	36.0	0.020
	Placebo	591	139	23.5	20.2	27.2	-	-	-	-
South Africa	HRV_2D	1057	49	4.6	3.4	6.1	43.4	18.7	61.0	<0.001
	HRV_3D	1059	43	4.1	3.0	5.4	50.4	27.7	66.4	<0.001
	HRV_POOL	2116	92	4.3	3.5	5.3	46.9	27.9	60.9	<0.001
	Placebo	1050	86	8.2	6.6	10.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 155 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by South Africa cohorts (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	15	2.5	1.4	4.0	70.2	46.1	84.5	<0.001
	HRV_3D	612	25	4.1	2.7	6.0	50.6	18.6	70.7	0.003
	HRV_POOL	1222	40	3.3	2.3	4.4	60.4	38.7	74.5	<0.001
	Placebo	605	50	8.3	6.2	10.8	-	-	-	-
2	HRV_2D	447	34	7.6	5.3	10.5	6.0	-54.6	42.9	0.805
	HRV_3D	447	18	4.0	2.4	6.3	50.2	10.0	73.4	0.012
	HRV_POOL	894	52	5.8	4.4	7.6	28.1	-13.2	53.9	0.128
	Placebo	445	36	8.1	5.7	11.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 156 Percentage of subjects hospitalized and/or treated re-hydration therapy due to RV GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	94	5.7	4.6	6.9	50.7	36.6	61.9	<0.001
HRV_3D	1651	75	4.5	3.6	5.7	60.8	48.5	70.4	<0.001
HRV_POOL	3298	169	5.1	4.4	5.9	55.7	45.3	64.2	<0.001
Placebo	1641	190	11.6	10.1	13.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 157 Percentage of subjects hospitalized due to RV GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	13	0.8	0.4	1.3	31.8	-45.5	69.1	0.293
HRV_3D	1651	7	0.4	0.2	0.9	63.4	9.0	87.0	0.018
HRV_POOL	3298	20	0.6	0.4	0.9	47.6	-3.7	73.5	0.059
Placebo	1641	19	1.2	0.7	1.8	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 158 Percentage of subjects hospitalized and/or treated re-hydration therapy due to GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	561	34.1	31.8	36.4	8.5	-2.8	18.6	0.058
HRV_3D	1651	520	31.5	29.3	33.8	15.4	4.8	24.9	<0.001
HRV_POOL	3298	1081	32.8	31.2	34.4	12.0	2.6	20.4	0.002
Placebo	1641	611	37.2	34.9	39.6	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 159 Percentage of subjects hospitalized due to GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	69	4.2	3.3	5.3	8.3	-28.8	34.9	0.610
HRV_3D	1651	49	3.0	2.2	3.9	35.1	5.7	55.6	0.017
HRV_POOL	3298	118	3.6	3.0	4.3	21.7	-6.0	41.9	0.101
Placebo	1641	75	4.6	3.6	5.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 160 Percentage of subjects reporting severe RV GE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by status of anti rotavirus IgA antibody concentration after dose 3 (Total vaccinated cohort)

				n/N			VE			
Status	Group	N	n	%	LL	UL	%	LL	UL	P-value
Negative	HRV_2D	513	19	3.7	2.2	5.7	20.4	-38.0	55.8	0.428
	HRV_3D	521	11	2.1	1.1	3.7	54.6	11.4	78.7	0.016
	HRV_POOL	1034	30	2.9	2.0	4.1	37.6	-0.5	61.8	0.038
	Placebo	1032	48	4.7	3.4	6.1	-	-	-	-
Positive	HRV_2D	914	14	1.5	0.8	2.6	80.3	61.0	90.4	<0.001
	HRV_3D	863	19	2.2	1.3	3.4	71.6	47.0	85.1	<0.001
	HRV_POOL	1777	33	1.9	1.3	2.6	76.1	58.6	86.0	<0.001
	Placebo	348	27	7.8	5.2	11.1	-	-	-	-
Unknown	HRV_2D	220	4	1.8	0.5	4.6	40.7	-121.4	86.9	0.559
	HRV_3D	267	1	0.4	0.0	2.1	87.8	8.9	99.7	0.019
	HRV_POOL	487	5	1.0	0.3	2.4	66.5	-16.1	91.4	0.073
	Placebo	261	8	3.1	1.3	5.9	-	-	-	-

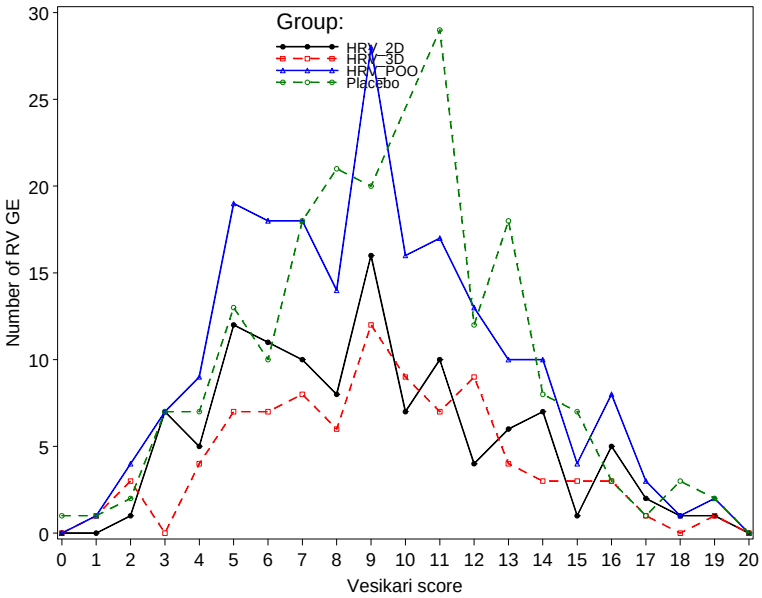
N = number of subjects included in each group
n (%) = number (percentage)s of subjects reporting severe RVGE episode, by status of anti rotavirus IgA antibodies concentration at visit 4
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 161 Percentage of subject reporting severe RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 6 by Cox (Total vaccinated cohort)

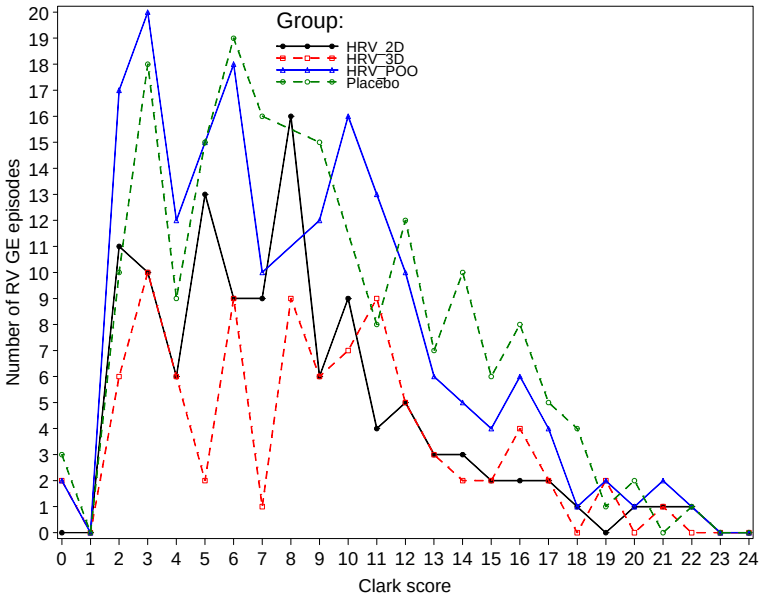
					Person-year rate			VE			
Event Type	Group	N	n	T (year)	n/T	LL	UL	%	LL	UL	P-VALUE
Severe RV GE of any type											
Any	HRV_2D	1647	37	1316.84	0.028	0.020	0.039	57.170	36.903	70.927	<0.001
	HRV_3D	1651	31	1296.80	0.024	0.017	0.034	63.493	44.849	75.834	<0.001
	HRV_POOL	3298	68	2613.64	0.026	0.021	0.033	60.318	45.321	71.202	<0.001
	Placebo	1641	83	1268.85	0.065	0.053	0.081	-	-	-	.
Severe RV GE of G1 wild type											
Any	HRV_2D	1647	9	1327.76	0.007	0.004	0.013	67.602	31.111	84.763	0.003
	HRV_3D	1651	9	1305.32	0.007	0.004	0.013	66.990	29.810	84.475	0.004
	HRV_POOL	3298	18	2633.08	0.007	0.004	0.011	67.328	40.681	82.005	<0.001
	Placebo	1641	27	1291.60	0.021	0.014	0.030	-	-	-	.
Severe RV GE of pooled Non G1 (G2, G3,...)											
Any	HRV_2D	1647	28	1320.53	0.021	0.015	0.031	51.657	23.905	69.288	0.002
	HRV_3D	1651	22	1299.36	0.017	0.011	0.026	61.281	36.598	76.355	<0.001
	HRV_POOL	3298	50	2619.88	0.019	0.014	0.025	56.440	36.216	70.252	<0.001
	Placebo	1641	56	1280.45	0.044	0.034	0.057	-	-	-	.

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)

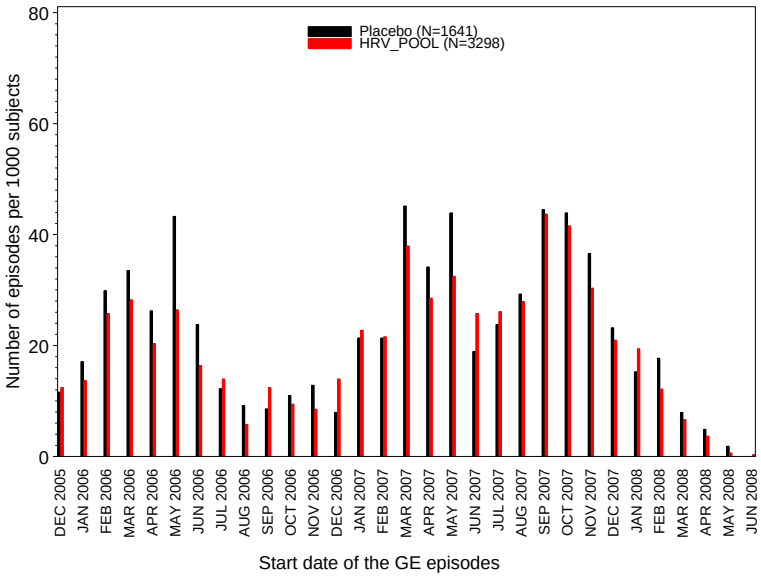
Supplement 162 Distribution of Vesikari score for RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6 (Total vaccinated cohort)



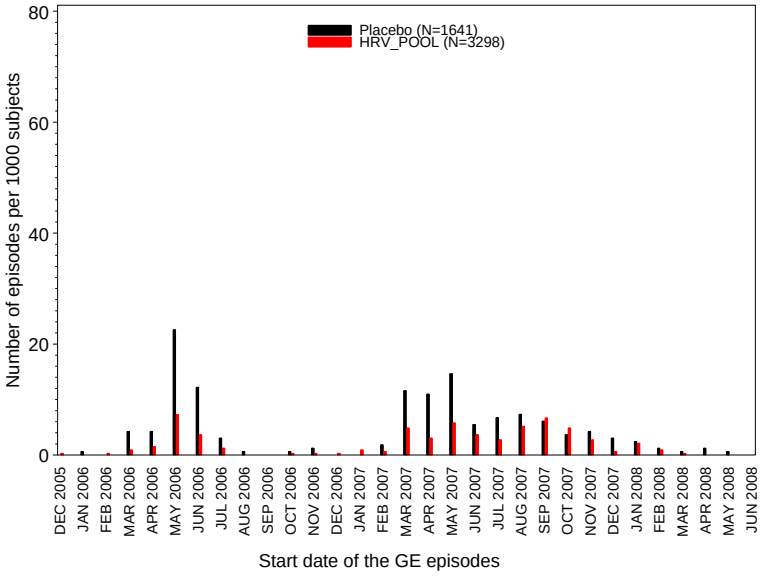
Supplement 163 Distribution of Clark score for RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to VISIT 6 (Total vaccinated cohort)



Supplement 164 Seasonal distribution of GE episode reported from Dose 1 of HRV vaccine or placebo up to VISIT 6 for pooled HRV groups and placebo group (Total vaccinated cohort)



Supplement 165 Seasonal distribution of RV GE episode reported from Dose 1 of HRV vaccine or placebo up to VISIT 6 for pooled HRV groups and placebo group (Total vaccinated cohort)



Supplement 166 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from dose 1 of HRV vaccine or placebo up to 14 days post Dose 3 of HRV vaccine or placebo (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Characteristics	Total number of episodes reported	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
GE	0	1389	84.3	1396	84.6	2785	84.4	1351	82.3	4136	83.7
	1	220	13.4	220	13.3	440	13.3	248	15.1	688	13.9
	2	32	1.9	32	1.9	64	1.9	37	2.3	101	2.0
	3	5	0.3	3	0.2	8	0.2	5	0.3	13	0.3
	4	1	0.1	0	0.0	1	0.0	0	0.0	1	0.0
	Any	258	15.7	255	15.4	513	15.6	290	17.7	803	16.3
RVGE	0	1627	98.8	1638	99.2	3265	99.0	1602	97.6	4867	98.5
	1	20	1.2	13	0.8	33	1.0	39	2.4	72	1.5
	Any	20	1.2	13	0.8	33	1.0	39	2.4	72	1.5
Severe GE	0	1613	97.9	1619	98.1	3232	98.0	1589	96.8	4821	97.6
	1	31	1.9	30	1.8	61	1.8	48	2.9	109	2.2
	2	3	0.2	2	0.1	5	0.2	4	0.2	9	0.2
	Any	34	2.1	32	1.9	66	2.0	52	3.2	118	2.4
Severe RVGE	0	1640	99.6	1646	99.7	3286	99.6	1628	99.2	4914	99.5
	1	7	0.4	5	0.3	12	0.4	13	0.8	25	0.5
	Any	7	0.4	5	0.3	12	0.4	13	0.8	25	0.5

N = number of subject included in each group, for considered efficacy follow-up period
n (%) = number (percentage) subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 167 Percentage of GE episodes with no available stool results from dose 1 of HRV vaccine or placebo up to 14 days post dose 3 (Total vaccinated cohort)

Category	HRV_2D N'=303		HRV_3D N'=293		HRV_POOL N'=596		Placebo N'=337	
	n	%	n	%	n	%	n	%
No stool results available	38	12.5	38	13.0	76	12.6	43	12.8
no stools collected	37	12.2	37	12.6	74	12.4	39	11.6
stools collected but no results available	1	0.3	1	0.3	2	0.3	4	1.2

N' = number of gastroenteritis episodes reported
n/percent = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 168 Number of GE episodes reported from dose 1 up to 14 days post Dose 3 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%	n	%	n	%
GE	Mild (1-6)	181	59.7	162	55.3	343	57.6	179	53.1
	Moderate (7-10)	78	25.7	93	31.7	171	28.7	96	28.5
	Severe (>10)	37	12.2	34	11.6	71	11.9	56	16.6
	Unknown	7	2.3	4	1.4	11	1.8	6	1.8
	Any	296	97.7	289	98.6	585	98.2	331	98.2
RV GE	Mild (1-6)	8	40.0	2	15.4	10	30.3	8	20.5
	Moderate (7-10)	5	25.0	6	46.2	11	33.3	18	46.2
	Severe (>10)	7	35.0	5	38.5	12	36.4	13	33.3
	Any	20	100	13	100	33	100	39	100

n (%) = number (percentage) of specified event reported in each group by severity using the 20-point Vesikari scale among all specified event reported during the considered efficacy period
Any= Any specified symptom reported and scored >0 in Vesikari severity scale
Unknown= symptom reported with Vesikari score =0

Supplement 169 Percentage of subjects with RV GE episodes from dose 1 up to 14 days post Dose 3 by G serotype and p genotype (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Serotype	n	%	n	%	n	%	n	%
Any	20	1.2	13	0.8	33	1.0	39	2.4
G1 vaccine type	3	0.2	1	0.1	4	0.1	0	0.0
G1 wild type	3	0.2	1	0.1	4	0.1	11	0.7
G2	2	0.1	1	0.1	3	0.1	4	0.2
G8	9	0.5	4	0.2	13	0.4	9	0.5
G9	0	0.0	1	0.1	1	0.0	1	0.1
GX	4	0.2	5	0.3	9	0.3	15	0.9
P4	10	0.6	3	0.2	13	0.4	13	0.8
P6	5	0.3	6	0.4	11	0.3	11	0.7
P8 vaccine type	3	0.2	1	0.1	4	0.1	0	0.0
P8 wild type	3	0.2	3	0.2	6	0.2	16	1.0

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 170 Percentage of subjects with severe RV GE episodes from dose 1 up to 14 days post Dose 3 by G serotype and P genotype (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Serotype	n	%	n	%	n	%	n	%
Any	7	0.4	5	0.3	12	0.4	13	0.8
G1 wild type	1	0.1	0	0.0	1	0.0	4	0.2
G2	1	0.1	0	0.0	1	0.0	0	0.0
G8	5	0.3	2	0.1	7	0.2	3	0.2
G9	0	0.0	0	0.0	0	0.0	1	0.1
GX	1	0.1	3	0.2	4	0.1	5	0.3
P4	5	0.3	1	0.1	6	0.2	3	0.2
P6	1	0.1	3	0.2	4	0.1	5	0.3
P8 wild type	1	0.1	1	0.1	2	0.1	6	0.4

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one severe RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 171 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post dose 3, by G and P type (Total vaccinated cohort)

Serotype	HRV_2D N'=20		HRV_3D N'=13		HRV_POOL N'=33		Placebo N'=39	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	3	15.00	1	7.69	4	12.12	0	0.00
G1WT+G2+P4	1	5.00	0	0.00	1	3.03	0	0.00
G1WT+G8+P8WT	0	0.00	0	0.00	0	0.00	1	2.56
G1WT+P8WT	2	10.00	1	7.69	3	9.09	10	25.64
G2+P4	1	5.00	1	7.69	2	6.06	4	10.26
G8+P4	7	35.00	2	15.38	9	27.27	8	20.51
G8+P4+P6	1	5.00	0	0.00	1	3.03	0	0.00
G8+P6	0	0.00	1	7.69	1	3.03	0	0.00
G8+P8WT	1	5.00	1	7.69	2	6.06	0	0.00
G9+P8WT	0	0.00	1	7.69	1	3.03	1	2.56
GX+P4	0	0.00	0	0.00	0	0.00	1	2.56
GX+P6	4	20.00	5	38.46	9	27.27	10	25.64
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	2.56
GX+P8WT	0	0.00	0	0.00	0	0.00	3	7.69

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3
GX=G12 Sero Type

Supplement 172 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 1)

Serotype	HRV_2D N'=1		HRV_3D N'=2		HRV_POOL N'=3		Placebo N'=5	
	n	%	n	%	N	%	n	%
G1VAC+P8VAC	1	100.0	1	50.00	2	66.67	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	3	60.00
G2+P4	0	0.00	0	0.00	0	0.00	1	20.00
G8+P4	0	0.00	0	0.00	0	0.00	1	20.00
G9+P8WT	0	0.00	1	50.00	1	33.33	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 173 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 2)

Serotype	HRV_2D N'=5		HRV_3D N'=1		HRV_POOL N'=6		Placebo N'=10	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	20.00	0	0.00	1	16.67	0	0.00
G1WT+G2+P4	1	20.00	0	0.00	1	16.67	0	0.00
G1WT+P8WT	1	20.00	1	100.0	2	33.33	7	70.00
G2+P4	1	20.00	0	0.00	1	16.67	3	30.00
GX+P6	1	20.00	0	0.00	1	16.67	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 174 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, South Africa)

Serotype	HRV_2D N'=6		HRV_3D N'=3		HRV_POOL N'=9		Placebo N'=15	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	2	33.33	1	33.33	3	33.33	0	0.00
G1WT+G2+P4	1	16.67	0	0.00	1	11.11	0	0.00
G1WT+P8WT	1	16.67	1	33.33	2	22.22	10	66.67
G2+P4	1	16.67	0	0.00	1	11.11	4	26.67
G8+P4	0	0.00	0	0.00	0	0.00	1	6.67
G9+P8WT	0	0.00	1	33.33	1	11.11	0	0.00
GX+P6	1	16.67	0	0.00	1	11.11	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 175 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, Malawi)

Serotype	HRV_2D N'=14		HRV_3D N'=10		HRV_POOL N'=24		Placebo N'=24	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	7.14	0	0.00	1	4.17	0	0.00
G1WT+G8+P8WT	0	0.00	0	0.00	0	0.00	1	4.17
G1WT+P8WT	1	7.14	0	0.00	1	4.17	0	0.00
G2+P4	0	0.00	1	10.00	1	4.17	0	0.00
G8+P4	7	50.00	2	20.00	9	37.50	7	29.17
G8+P4+P6	1	7.14	0	0.00	1	4.17	0	0.00
G8+P6	0	0.00	1	10.00	1	4.17	0	0.00
G8+P8WT	1	7.14	1	10.00	2	8.33	0	0.00
G9+P8WT	0	0.00	0	0.00	0	0.00	1	4.17
GX+P4	0	0.00	0	0.00	0	0.00	1	4.17
GX+P6	3	21.43	5	50.00	8	33.33	10	41.67
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	4.17
GX+P8WT	0	0.00	0	0.00	0	0.00	3	12.50

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3
GX=G12 Sero Type

Supplement 176 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post dose 3, by G and P type (Total vaccinated cohort)

Serotype	HRV_2D N'=7		HRV_3D N'=5		HRV_POOL N'=12		Placebo N'=13	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	14.29	0	0.00	1	8.33	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	4	30.77
G8+P4	4	57.14	1	20.00	5	41.67	3	23.08
G8+P8WT	1	14.29	1	20.00	2	16.67	0	0.00
G9+P8WT	0	0.00	0	0.00	0	0.00	1	7.69
GX+P6	1	14.29	3	60.00	4	33.33	4	30.77
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	7.69

n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3
Any = any specified symptom reported, regardless of the serotype
GX=G12 Sero Type

Supplement 177 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 1)

Serotype	HRV_2D N'=0		HRV_3D N'=0		HRV_POOL N'=0		Placebo N'=1	
	n	%	n	%	n	%	n	%
G1WT+P8WT	0	0.00	0	0.00	0	0.00	1	100.0

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 178 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 2)

Serotype	HRV_2D N'=1		HRV_3D N'=0		HRV_POOL N'=1		Placebo N'=3	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	100.0	0	0.00	1	100.0	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	3	100.0

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 179 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, South Africa)

Serotype	HRV_2D N'=1		HRV_3D N'=0		HRV_POOL N'=1		Placebo N'=4	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	100.0	0	0.00	1	100.0	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	4	100.0

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 180 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to 14 days post Dose 3, by G and P type (Total vaccinated cohort, Severe RVGE episode - Malawi)

Serotype	HRV_2D N'=6		HRV_3D N'=5		HRV_POOL N'=11		Placebo N'=9	
	n	%	n	%	n	%	n	%
G8+P4	4	66.67	1	20.00	5	45.45	3	33.33
G8+P8WT	1	16.67	1	20.00	2	18.18	0	0.00
G9+P8WT	0	0.00	0	0.00	0	0.00	1	11.11
GX+P6	1	16.67	3	60.00	4	36.36	4	44.44
GX+P6+P8WT	0	0.00	0	0.00	0	0.00	1	11.11

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to 14 days post dose 3

Supplement 181 Duration (in years) of efficacy follow-up period - from Dose 1 up to 14 days post Dose 3 - (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 1647	HRV_3D N = 1651	HRV_POOL N = 3298	Placebo N = 1641
	Value or n	Value or n	Value or n	Value or n
Total	376.9	377.5	754.4	381.5
Mean	0.23	0.23	0.23	0.23
Minimum	0.04	0.04	0.04	0.04
Q1	0.22	0.22	0.22	0.22
Median	0.23	0.23	0.23	0.23
Q3	0.24	0.24	0.24	0.24
Maximum	1.13	1.07	1.13	1.07

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 182 Duration (in years) of efficacy follow-up period - from Dose 1 up to 14 days post Dose 3 – South Africa Cohort 2 (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 447	HRV_3D N = 447	HRV_POOL N = 894	Placebo N = 445
	Value or n	Value or n	Value or n	Value or n
Total	100.9	102.1	203.1	102.9
Mean	0.23	0.23	0.23	0.23
Minimum	0.04	0.04	0.04	0.04
Q1	0.21	0.21	0.21	0.21
Median	0.23	0.23	0.23	0.23
Q3	0.24	0.24	0.24	0.24
Maximum	0.94	0.91	0.94	1.00

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 183 Duration (in years) of efficacy follow-up period - from Dose 1 up to 14 days post Dose 3 – South Africa Cohort 1 (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 610	HRV_3D N = 612	HRV_POOL N = 1222	Placebo N = 605
	Value or n	Value or n	Value or n	Value or n
Total	140.7	141.1	281.9	141.2
Mean	0.23	0.23	0.23	0.23
Minimum	0.04	0.04	0.04	0.04
Q1	0.21	0.21	0.21	0.21
Median	0.23	0.23	0.23	0.23
Q3	0.24	0.24	0.24	0.24
Maximum	1.13	1.07	1.13	1.07

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 184 Duration (in years) of efficacy follow-up period - from Dose 1 up to 14 days post Dose 3 - South Africa (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 1057	HRV_3D N = 1059	HRV_POOL N = 2116	Placebo N = 1050
	Value or n	Value or n	Value or n	Value or n
Total	241.7	243.3	484.9	244.1
Mean	0.23	0.23	0.23	0.23
Minimum	0.04	0.04	0.04	0.04
Q1	0.21	0.21	0.21	0.21
Median	0.23	0.23	0.23	0.23
Q3	0.24	0.24	0.24	0.24
Maximum	1.13	1.07	1.13	1.07

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 185 Duration (in years) of efficacy follow-up period - from Dose 1 up to 14 days post Dose 3 - Malawi (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 590	HRV_3D N = 592	HRV_POOL N = 1182	Placebo N = 591
	Value or n	Value or n	Value or n	Value or n
Total	135.3	134.2	269.5	137.4
Mean	0.23	0.23	0.23	0.23
Minimum	0.04	0.04	0.04	0.04
Q1	0.23	0.23	0.23	0.23
Median	0.23	0.23	0.23	0.23
Q3	0.24	0.24	0.24	0.24
Maximum	0.41	0.93	0.93	0.92

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 186 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from Dose 1 up to 14 days post Dose 3 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	20	1.2	0.7	1.9	48.9	10.2	71.8	0.013
HRV_3D	1651	13	0.8	0.4	1.3	66.9	36.6	83.8	<0.001
HRV_POOL	3298	33	1.0	0.7	1.4	57.9	31.3	74.3	<0.001
Placebo	1641	39	2.4	1.7	3.2	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 187 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from Dose 1 up to 14 days post Dose 3 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	14	2.4	1.3	3.9	41.6	-17.6	72.1	0.137
	HRV_3D	592	10	1.7	0.8	3.1	58.4	9.8	82.2	0.015
	HRV_POOL	1182	24	2.0	1.3	3.0	50.0	8.1	72.8	0.019
	Placebo	591	24	4.1	2.6	6.0	-	-	-	-
South Africa	HRV_2D	1057	6	0.6	0.2	1.2	60.3	-8.4	87.4	0.051
	HRV_3D	1059	3	0.3	0.1	0.8	80.2	29.9	96.3	0.004
	HRV_POOL	2116	9	0.4	0.2	0.8	70.2	27.4	88.5	0.004
	Placebo	1050	15	1.4	0.8	2.3	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 188 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from Dose 1 up to 14 days post Dose 3 by South Africa cohort (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	1	0.2	0.0	0.9	80.2	-77.3	99.6	0.123
	HRV_3D	612	2	0.3	0.0	1.2	60.5	-141.5	96.2	0.285
	HRV_POOL	1222	3	0.2	0.1	0.7	70.3	-52.7	95.4	0.125
	Placebo	605	5	0.8	0.3	1.9	-	-	-	-
2	HRV_2D	447	5	1.1	0.4	2.6	50.2	-59.8	86.7	0.205
	HRV_3D	447	1	0.2	0.0	1.2	90.0	30.0	99.8	0.006
	HRV_POOL	894	6	0.7	0.2	1.5	70.1	9.3	91.1	0.017
	Placebo	445	10	2.2	1.1	4.1	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 189 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 14 days post Dose 3 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	7	0.4	0.2	0.9	46.4	-44.7	81.9	0.187
HRV_3D	1651	5	0.3	0.1	0.7	61.8	-14.3	89.3	0.062
HRV_POOL	3298	12	0.4	0.2	0.6	54.1	-9.2	80.8	0.055
Placebo	1641	13	0.8	0.4	1.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 190 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 14 days post Dose 3 by South Africa cohort (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	0	0.0	0.0	0.6	100.0	-3768.0	100.0	0.498
	HRV_3D	612	0	0.0	0.0	0.6	100.0	-3755.4	100.0	0.497
	HRV_POOL	1222	0	0.0	0.0	0.3	100.0	-1830.9	100.0	0.331
	Placebo	605	1	0.2	0.0	0.9	-	-	-	-
2	HRV_2D	447	1	0.2	0.0	1.2	66.8	-313.3	99.4	0.373
	HRV_3D	447	0	0.0	0.0	0.8	100.0	-140.9	100.0	0.124
	HRV_POOL	894	1	0.1	0.0	0.6	83.4	-106.6	99.7	0.110
	Placebo	445	3	0.7	0.1	2.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 191 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 14 days post Dose 3 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	6	1.0	0.4	2.2	33.2	-110.1	80.4	0.605
	HRV_3D	592	5	0.8	0.3	2.0	44.5	-84.3	85.4	0.299
	HRV_POOL	1182	11	0.9	0.5	1.7	38.9	-66.8	77.0	0.339
	Placebo	591	9	1.5	0.7	2.9	-	-	-	-
South Africa	HRV_2D	1057	1	0.1	0.0	0.5	75.2	-151.0	99.5	0.217
	HRV_3D	1059	0	0.0	0.0	0.3	100.0	-50.2	100.0	0.061
	HRV_POOL	2116	1	0.0	0.0	0.3	87.6	-25.4	99.7	0.044
	Placebo	1050	4	0.4	0.1	1.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 192 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to before Dose 3 (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Characteristics	Number of Episode	n	%	n	%	n	%	n	%
GE	0	1424	86.5	1424	86.3	2848	86.4	1402	85.4
	1	195	11.8	204	12.4	399	12.1	207	12.6
	2	22	1.3	21	1.3	43	1.3	28	1.7
	3	5	0.3	2	0.1	7	0.2	4	0.2
	4	1	0.1	0	0.0	1	0.0	0	0.0
	Any	223	13.5	227	13.7	450	13.6	239	14.6
RVGE	0	1631	99.0	1639	99.3	3270	99.2	1614	98.4
	1	16	1.0	12	0.7	28	0.8	27	1.6
	Any	16	1.0	12	0.7	28	0.8	27	1.6
Severe GE	0	1621	98.4	1620	98.1	3241	98.3	1600	97.5
	1	23	1.4	30	1.8	53	1.6	37	2.3
	2	3	0.2	1	0.1	4	0.1	4	0.2
	Any	26	1.6	31	1.9	57	1.7	41	2.5
Severe RVGE	0	1641	99.6	1647	99.8	3288	99.7	1633	99.5
	1	6	0.4	4	0.2	10	0.3	8	0.5
	Any	6	0.4	4	0.2	10	0.3	8	0.5

N = number of subject included in each group, for considered efficacy follow-up period
n (%) = number (percentage) subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified episode

Supplement 193 Percentage of GE episodes with no available stool results from dose 1 of HRV vaccine or placebo up to before dose 3 (Total vaccinated cohort)

Category	HRV_2D N'=258		HRV_3D N'=252		HRV_POOL N'=510		Placebo N'=275	
LABEL	n	%	n	%	n	%	n	%
No stool results available	30	11.6	30	11.9	60	11.8	34	12.4
no stools collected	30	11.6	29	11.5	59	11.6	31	11.3
stools collected but no results available	0	0.0	1	0.4	1	0.2	3	1.1

N' = number of gastroenteritis episodes reported
n (percent) = number (percentage) of gastroenteritis episodes reported with the specified category

Supplement 194 Number of GE episodes reported from Dose 1 up to before Dose 3 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

		HRV_2D		HRV_3D		HRV_POOL		Placebo	
Event	Severity using 20 point Vesikari scale	n	%	n	%	n	%	n	%
GE	Mild (1-6)	157	60.9	140	55.6	297	58.2	149	54.2
	Moderate (7-10)	66	25.6	76	30.2	142	27.8	76	27.6
	Severe (>10)	29	11.2	32	12.7	61	12.0	45	16.4
	Unknown	6	2.3	4	1.6	10	2.0	5	1.8
	Any	252	97.7	248	98.4	500	98.0	270	98.2
RV GE	Mild (1-6)	7	43.8	2	16.7	9	32.1	7	25.9
	Moderate (7-10)	3	18.8	6	50.0	9	32.1	12	44.4
	Severe (>10)	6	37.5	4	33.3	10	35.7	8	29.6
	Any	16	100	12	100	28	100	27	100

n (%) = number (percentage) of specified event reported in each group by severity using the 20-point Vesikari scale among all specified event reported the considered efficacy period
Any= Any specified symptom reported and scored >0 in Vesikari severity scale
Unknown= symptom reported with vesikari score =0

Supplement 195 Percentage of subjects with RV GE episodes from Dose 1 up to before Dose 3 by G serotype and p genotype (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Serotype	n	%	n	%	n	%	n	%
Any	16	1.0	12	0.7	28	0.8	27	1.6
G1 vaccine type	2	0.1	1	0.1	3	0.1	0	0.0
G1 wild type	2	0.1	1	0.1	3	0.1	6	0.4
G2	1	0.1	1	0.1	2	0.1	2	0.1
G8	8	0.5	4	0.2	12	0.4	7	0.4
G9	0	0.0	1	0.1	1	0.0	1	0.1
GX	4	0.2	4	0.2	8	0.2	12	0.7
P4	9	0.5	3	0.2	12	0.4	8	0.5
P6	5	0.3	5	0.3	10	0.3	9	0.5
P8 vaccine type	2	0.1	1	0.1	3	0.1	0	0.0
P8 wild type	1	0.1	3	0.2	4	0.1	10	0.6

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 196 Percentage of subjects with severe RV GE episodes from Dose 1 up to before Dose 3 by G serotype and P genotype (Total vaccinated cohort)

	HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641	
Serotype	n	%	n	%	n	%	n	%
Any	6	0.4	4	0.2	10	0.3	8	0.5
G1 wild type	1	0.1	0	0.0	1	0.0	2	0.1
G2	1	0.1	0	0.0	1	0.0	0	0.0
G8	4	0.2	2	0.1	6	0.2	2	0.1
G9	0	0.0	0	0.0	0	0.0	1	0.1
GX	1	0.1	2	0.1	3	0.1	3	0.2
P4	5	0.3	1	0.1	6	0.2	2	0.1
P6	1	0.1	2	0.1	3	0.1	3	0.2
P8 wild type	0	0.0	1	0.1	1	0.0	3	0.2

N = number of subjects included in each group
n (%) = number (percentage) of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one severe RV GE episode whatever the serotype
GX=G12 Sero Type

Supplement 197 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort)

Serotype	HRV_2D N'=16		HRV_3D N'=12		HRV_POOL N'=28		Placebo N'=27	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	2	12.50	1	8.33	3	10.71	0	0.00
G1WT+G2+P4	1	6.25	0	0.00	1	3.57	0	0.00
G1WT+G8+P8WT	0	0.00	0	0.00	0	0.00	1	3.70
G1WT+P8WT	1	6.25	1	8.33	2	7.14	5	18.52
G2+P4	0	0.00	1	8.33	1	3.57	2	7.41
G8+P4	7	43.75	2	16.67	9	32.14	6	22.22
G8+P4+P6	1	6.25	0	0.00	1	3.57	0	0.00
G8+P6	0	0.00	1	8.33	1	3.57	0	0.00
G8+P8WT	0	0.00	1	8.33	1	3.57	0	0.00
G9+P8WT	0	0.00	1	8.33	1	3.57	1	3.70
GX+P6	4	25.00	4	33.33	8	28.57	9	33.33
GX+P8WT	0	0.00	0	0.00	0	0.00	3	11.11

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from dose 1 of HRV vaccine or placebo up to before dose 3
GX=G12 Sero Type

Supplement 198 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, South Africa)

Serotype	HRV_2D N'=3		HRV_3D N'=3		HRV_POOL N'=6		Placebo N'=7	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	33.33	1	33.33	2	33.33	0	0.00
G1WT+G2+P4	1	33.33	0	0.00	1	16.67	0	0.00
G1WT+P8WT	0	0.00	1	33.33	1	16.67	5	71.43
G2+P4	0	0.00	0	0.00	0	0.00	2	28.57
G9+P8WT	0	0.00	1	33.33	1	16.67	0	0.00
GX+P6	1	33.33	0	0.00	1	16.67	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3
GX=G12 Sero Type

Supplement 199 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 1)

Serotype	HRV_2D N'=1		HRV_3D N'=2		HRV_POOL N'=3		Placebo N'=1	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	100.0	1	50.00	2	66.67	0	0.00
G2+P4	0	0.00	0	0.00	0	0.00	1	100.0
G9+P8WT	0	0.00	1	50.00	1	33.33	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3

Supplement 200 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 2)

Serotype	HRV_2D N'=2		HRV_3D N'=1		HRV_POOL N'=3		Placebo N'=6	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	50.00	0	0.00	1	33.33	0	0.00
G1WT+P8WT	0	0.00	1	100.0	1	33.33	5	83.33
G2+P4	0	0.00	0	0.00	0	0.00	1	16.67
GX+P6	1	50.00	0	0.00	1	33.33	0	0.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3
GX=G12 Sero Type

Supplement 201 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, Malawi)

Serotype	HRV_2D N'=13		HRV_3D N'=9		HRV_POOL N'=22		Placebo N'=20	
	n	%	n	%	n	%	n	%
G1VAC+P8VAC	1	7.69	0	0.00	1	4.55	0	0.00
G1WT+G8+P8WT	0	0.00	0	0.00	0	0.00	1	5.00
G1WT+P8WT	1	7.69	0	0.00	1	4.55	0	0.00
G2+P4	0	0.00	1	11.11	1	4.55	0	0.00
G8+P4	7	53.85	2	22.22	9	40.91	6	30.00
G8+P4+P6	1	7.69	0	0.00	1	4.55	0	0.00
G8+P6	0	0.00	1	11.11	1	4.55	0	0.00
G8+P8WT	0	0.00	1	11.11	1	4.55	0	0.00
G9+P8WT	0	0.00	0	0.00	0	0.00	1	5.00
GX+P6	3	23.08	4	44.44	7	31.82	9	45.00
GX+P8WT	0	0.00	0	0.00	0	0.00	3	15.00

N'= Number of RV GE episodes reported
n (%) = number (percentage) of RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3
GX=G12 Sero Type

Supplement 202 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort)

Serotype	HRV_2D N'=6		HRV_3D N'=4		HRV_POOL N'=10		Placebo N'=8	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	16.67	0	0.00	1	10.00	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	2	25.00
G8+P4	4	66.67	1	25.00	5	50.00	2	25.00
G8+P8WT	0	0.00	1	25.00	1	10.00	0	0.00
G9+P8WT	0	0.00	0	0.00	0	0.00	1	12.50
GX+P6	1	16.67	2	50.00	3	30.00	3	37.50

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3
GX=G12 Sero Type

Supplement 203 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, Malawi)

Serotype	HRV_2D N'=5		HRV_3D N'=4		HRV_POOL N'=9		Placebo N'=6	
	n	%	n	%	n	%	n	%
G8+P4	4	80.00	1	25.00	5	55.56	2	33.33
G8+P8WT	0	0.00	1	25.00	1	11.11	0	0.00
G9+P8WT	0	0.00	0	0.00	0	0.00	1	16.67
GX+P6	1	20.00	2	50.00	3	33.33	3	50.00

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3
GX=G12 Sero Type

Supplement 204 Number of severe RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort)

Serotype	HRV_2D N'=1		HRV_3D N'=0		HRV_POOL N'=1		Placebo N'=2	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	100.0	0	0.00	1	100.0	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	2	100.0

N'= Number of severe RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3

Supplement 205 Number of RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3, by G and P type (Total vaccinated cohort, South Africa cohort 2)

Serotype	HRV_2D N'=1		HRV_3D N'=0		HRV_POOL N'=1		Placebo N'=2	
	n	%	n	%	n	%	n	%
G1WT+G2+P4	1	100.0	0	0.00	1	100.0	0	0.00
G1WT+P8WT	0	0.00	0	0.00	0	0.00	2	100.0

N'= Number of RV GE episodes reported
n (%) = number (percentage) of severe RV GE episodes reporting the specified serotype in each group, among all RV GE episodes reported from Dose 1 of HRV vaccine or placebo up to before Dose 3
Samples collected in case of gastroenteritis episodes from the first dose and the last visit

Supplement 206 Duration (in years) of efficacy follow-up period - from Dose 1 up to before Dose 3 - (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 1647	HRV_3D N = 1651	HRV_POOL N = 3298	Placebo N = 1641
	Value or n	Value or n	Value or n	Value or n
Total	309.3	309.7	618.9	314.1
Mean	0.19	0.19	0.19	0.19
Minimum	0.00	0.00	0.00	0.00
Q1	0.18	0.18	0.18	0.18
Median	0.19	0.19	0.19	0.19
Q3	0.19	0.19	0.19	0.20
Maximum	1.09	1.03	1.09	1.02

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 207 Duration (in years) of efficacy follow-up period - from Dose 1 up to before Dose 3 - Cohort 1 (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 610	HRV_3D N = 612	HRV_POOL N = 1222	Placebo N = 605
Parameters or Categories	Value or n	Value or n	Value or n	Value or n
Total	115.7	116.0	231.7	116.4
Mean	0.19	0.19	0.19	0.19
Minimum	0.00	0.00	0.00	0.00
Q1	0.17	0.17	0.17	0.17
Median	0.19	0.19	0.19	0.19
Q3	0.20	0.20	0.20	0.20
Maximum	1.09	1.03	1.09	1.02

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 208 Duration (in years) of efficacy follow-up period - from Dose 1 up to before Dose 3 - South Africa (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 1057	HRV_3D N = 1059	HRV_POOL N = 2116	Placebo N = 1050
Parameters or Categories	Value or n	Value or n	Value or n	Value or n
Total	198.2	199.8	398.0	201.0
Mean	0.19	0.19	0.19	0.19
Minimum	0.00	0.00	0.00	0.00
Q1	0.17	0.17	0.17	0.17
Median	0.19	0.19	0.19	0.19
Q3	0.19	0.20	0.20	0.20
Maximum	1.09	1.03	1.09	1.02

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 209 Duration (in years) of efficacy follow-up period - from Dose 1 up to before Dose 3 - Cohort 2 South Africa (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 447	HRV_3D N = 447	HRV_POOL N = 894	Placebo N = 445
Parameters or Categories	Value or n	Value or n	Value or n	Value or n
Total	82.58	83.76	166.3	84.65
Mean	0.18	0.19	0.19	0.19
Minimum	0.00	0.00	0.00	0.00
Q1	0.17	0.17	0.17	0.17
Median	0.19	0.19	0.19	0.19
Q3	0.19	0.19	0.19	0.20
Maximum	0.90	0.87	0.90	0.96

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 210 Duration (in years) of efficacy follow-up period - from Dose 1 up to before Dose 3 - Malawi (Total vaccinated cohort)

Duration (years) of follow up period	HRV_2D N = 590	HRV_3D N = 592	HRV_POOL N = 1182	Placebo N = 591
Parameters or Categories	Value or n	Value or n	Value or n	Value or n
Total	111.0	109.9	220.9	113.1
Mean	0.19	0.19	0.19	0.19
Minimum	0.00	0.00	0.00	0.00
Q1	0.19	0.19	0.19	0.19
Median	0.19	0.19	0.19	0.19
Q3	0.19	0.19	0.19	0.19
Maximum	0.37	0.89	0.89	0.88

N = number of subject included in each group
Total= sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 211 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from Dose 1 up to before Dose 3 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	16	1.0	0.6	1.6	41.0	-13.6	70.3	0.093
HRV_3D	1651	12	0.7	0.4	1.3	55.8	9.8	79.6	0.016
HRV_POOL	3298	28	0.8	0.6	1.2	48.4	9.0	70.7	0.014
Placebo	1641	27	1.6	1.1	2.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 212 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from Dose 1 up to before Dose 3 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	13	2.2	1.2	3.7	34.9	-37.5	70.2	0.289
	HRV_3D	592	9	1.5	0.7	2.9	55.1	-3.2	82.0	0.040
	HRV_POOL	1182	22	1.9	1.2	2.8	45.0	-6.2	71.4	0.067
	Placebo	591	20	3.4	2.1	5.2	-	-	-	-
South Africa	HRV_2D	1057	3	0.3	0.1	0.8	57.4	-86.5	92.9	0.224
	HRV_3D	1059	3	0.3	0.1	0.8	57.5	-86.1	92.9	0.224
	HRV_POOL	2116	6	0.3	0.1	0.6	57.5	-47.8	88.2	0.140
	Placebo	1050	7	0.7	0.3	1.4	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 213 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from Dose 1 up to before Dose 3 by South Africa cohort (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	1	0.2	0.0	0.9	0.8	-7685.3	98.7	1.000
	HRV_3D	612	2	0.3	0.0	1.2	-97.7	-11564.5	89.7	1.000
	HRV_POOL	1222	3	0.2	0.1	0.7	-48.5	-7697.3	88.1	1.000
	Placebo	605	1	0.2	0.0	0.9	-	-	-	-
2	HRV_2D	447	2	0.4	0.1	1.6	66.8	-85.6	96.7	0.177
	HRV_3D	447	1	0.2	0.0	1.2	83.4	-36.8	99.6	0.069
	HRV_POOL	894	3	0.3	0.1	1.0	75.1	-16.5	96.0	0.067
	Placebo	445	6	1.3	0.5	2.9	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 214 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from Dose 1 up to before Dose 3 (Total vaccinated cohort)

			n/N			VE			
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	1647	6	0.4	0.1	0.8	25.3	-145.6	78.6	0.606
HRV_3D	1651	4	0.2	0.1	0.6	50.3	-85.5	89.0	0.265
HRV_POOL	3298	10	0.3	0.1	0.6	37.8	-81.3	77.9	0.323
Placebo	1641	8	0.5	0.2	1.0	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 215 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from Dose 1 up to before Dose 3 by South Africa cohorts (Total vaccinated cohort)

				n/N			VE			
Cohort	Group	N	n	%	LL	UL	%	LL	UL	P-value
1	HRV_2D	610	0	0.0	0.0	0.6	.	.	.	-
	HRV_3D	612	0	0.0	0.0	0.6	.	.	.	-
	HRV_POOL	1222	0	0.0	0.0	0.3	.	.	.	-
	Placebo	605	0	0.0	0.0	0.6	-	-	-	-
2	HRV_2D	447	1	0.2	0.0	1.2	50.2	-856.2	99.2	0.624
	HRV_3D	447	0	0.0	0.0	0.8	100.0	-430.1	100.0	0.249
	HRV_POOL	894	1	0.1	0.0	0.6	75.1	-378.1	99.6	0.258
	Placebo	445	2	0.4	0.1	1.6	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 216 Percentage of subjects reporting severe (Vesikari score equal to or greater than 11) RV GE episode and efficacy of the vaccine from Dose 1 up to before Dose 3 by country (Total vaccinated cohort)

				n/N			VE			
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	590	5	0.8	0.3	2.0	16.5	-228.3	79.8	1.000
	HRV_3D	592	4	0.7	0.2	1.7	33.4	-180.7	86.2	0.547
	HRV_POOL	1182	9	0.8	0.3	1.4	25.0	-156.1	76.2	0.589
	Placebo	591	6	1.0	0.4	2.2	-	-	-	-
South Africa	HRV_2D	1057	1	0.1	0.0	0.5	50.3	-854.1	99.2	0.624
	HRV_3D	1059	0	0.0	0.0	0.3	100.0	-427.9	100.0	0.248
	HRV_POOL	2116	1	0.0	0.0	0.3	75.2	-376.6	99.6	0.257
	Placebo	1050	2	0.2	0.0	0.7	-	-	-	-

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
n/N (%) = percentage of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Supplement 217 Listing of SAEs (Total vaccinated cohort)

[redacted]

Supplement 218 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 1)

	HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	53	8.7	6.6	11.2	38	6.2	4.4	8.4	91	7.4	6.0	9.1	62	10.2	7.9	12.9
Blood and lymphatic system disorders (10005329)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	0	0.0	0.0	0.6
Cardiac disorders (10007541)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	2	0.2	0.0	0.6	0	0.0	0.0	0.6
Congenital, familial and genetic disorders (10010331)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	1	0.2	0.0	0.9
Eye disorders (10015919)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Gastrointestinal disorders (10017947)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	3	0.5	0.1	1.4
General disorders and administration site conditions (10018065)	1	0.2	0.0	0.9	3	0.5	0.1	1.4	4	0.3	0.1	0.8	3	0.5	0.1	1.4
Infections and infestations (10021881)	48	7.9	5.9	10.3	33	5.4	3.7	7.5	81	6.6	5.3	8.2	50	8.3	6.2	10.8
Injury, poisoning and procedural complications (10022117)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.2	0.1	0.7	4	0.7	0.2	1.7
Metabolism and nutrition disorders (10027433)	5	0.8	0.3	1.9	3	0.5	0.1	1.4	8	0.7	0.3	1.3	4	0.7	0.2	1.7
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Nervous system disorders (10029205)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	2	0.3	0.0	1.2
Renal and urinary	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6

	HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
disorders (10038359)																
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.3	0.0	1.2	2	0.3	0.0	1.2	4	0.3	0.1	0.8	4	0.7	0.2	1.7
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 219 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 2 South Africa)

	HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	29	6.5	4.4	9.2	29	6.5	4.4	9.2	58	6.5	5.0	8.3	34	7.6	5.3	10.5
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	1	0.2	0.0	1.2
Gastrointestinal disorders (10017947)	1	0.2	0.0	1.2	1	0.2	0.0	1.2	2	0.2	0.0	0.8	2	0.4	0.1	1.6
General disorders and administration site conditions (10018065)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	2	0.4	0.1	1.6
Infections and infestations (10021881)	28	6.3	4.2	8.9	24	5.4	3.5	7.9	52	5.8	4.4	7.6	30	6.7	4.6	9.5
Metabolism and nutrition disorders (10027433)	0	0.0	0.0	0.8	2	0.4	0.1	1.6	2	0.2	0.0	0.8	3	0.7	0.1	2.0
Nervous system disorders (10029205)	1	0.2	0.0	1.2	3	0.7	0.1	1.9	4	0.4	0.1	1.1	4	0.9	0.2	2.3
Respiratory, thoracic and mediastinal disorders (10038738)	1	0.2	0.0	1.2	3	0.7	0.1	1.9	4	0.4	0.1	1.1	0	0.0	0.0	0.8
Surgical and medical procedures (10042613)	1	0.2	0.0	1.2	0	0.0	0.0	0.8	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Vascular disorders (10047065)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 220 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, South Africa)

	HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	82	7.8	6.2	9.5	67	6.3	4.9	8.0	149	7.0	6.0	8.2	96	9.1	7.5	11.1
Blood and lymphatic system disorders (10005329)	2	0.2	0.0	0.7	1	0.1	0.0	0.5	3	0.1	0.0	0.4	1	0.1	0.0	0.5
Cardiac disorders (10007541)	1	0.1	0.0	0.5	1	0.1	0.0	0.5	2	0.1	0.0	0.3	0	0.0	0.0	0.4
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	1	0.1	0.0	0.5
Eye disorders (10015919)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Gastrointestinal disorders (10017947)	1	0.1	0.0	0.5	1	0.1	0.0	0.5	2	0.1	0.0	0.3	5	0.5	0.2	1.1
General disorders and administration site conditions (10018065)	1	0.1	0.0	0.5	4	0.4	0.1	1.0	5	0.2	0.1	0.6	5	0.5	0.2	1.1
Infections and infestations (10021881)	76	7.2	5.7	8.9	57	5.4	4.1	6.9	133	6.3	5.3	7.4	80	7.6	6.1	9.4
Injury, poisoning and procedural complications (10022117)	2	0.2	0.0	0.7	1	0.1	0.0	0.5	3	0.1	0.0	0.4	4	0.4	0.1	1.0
Metabolism and nutrition disorders (10027433)	5	0.5	0.2	1.1	5	0.5	0.2	1.1	10	0.5	0.2	0.9	7	0.7	0.3	1.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Nervous system disorders (10029205)	1	0.1	0.0	0.5	4	0.4	0.1	1.0	5	0.2	0.1	0.6	6	0.6	0.2	1.2
Renal and urinary	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4

	HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
disorders (10038359)																
Respiratory, thoracic and mediastinal disorders (10038738)	3	0.3	0.1	0.8	5	0.5	0.2	1.1	8	0.4	0.2	0.7	4	0.4	0.1	1.0
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
Surgical and medical procedures (10042613)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Vascular disorders (10047065)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 221 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Malawi)

	HRV_2D N = 590				HRV_3D N = 592				HRV_POOL N = 1182				Placebo N = 591			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	88	14.9	12.1	18.0	82	13.9	11.2	16.9	170	14.4	12.4	16.5	93	15.7	12.9	18.9
Blood and lymphatic system disorders (10005329)	1	0.2	0.0	0.9	4	0.7	0.2	1.7	5	0.4	0.1	1.0	3	0.5	0.1	1.5
Congenital, familial and genetic disorders (10010331)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Gastrointestinal disorders (10017947)	5	0.8	0.3	2.0	2	0.3	0.0	1.2	7	0.6	0.2	1.2	1	0.2	0.0	0.9
General disorders and administration site conditions (10018065)	1	0.2	0.0	0.9	3	0.5	0.1	1.5	4	0.3	0.1	0.9	1	0.2	0.0	0.9
Immune system disorders (10021428)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
Infections and infestations (10021881)	84	14.2	11.5	17.3	78	13.2	10.6	16.2	162	13.7	11.8	15.8	91	15.4	12.6	18.6
Injury, poisoning and procedural complications (10022117)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	2	0.3	0.0	1.2
Metabolism and nutrition disorders (10027433)	5	0.8	0.3	2.0	2	0.3	0.0	1.2	7	0.6	0.2	1.2	5	0.8	0.3	2.0
Nervous system disorders (10029205)	2	0.3	0.0	1.2	4	0.7	0.2	1.7	6	0.5	0.2	1.1	4	0.7	0.2	1.7
Respiratory, thoracic and mediastinal disorders (10038738)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	2	0.2	0.0	0.6	2	0.3	0.0	1.2
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 222 Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	8	0.5	0.2	1.0	13	0.8	0.4	1.3	21	0.6	0.4	1.0	5	0.3	0.1	0.7
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3
Infections and infestations (10021881)	8	0.5	0.2	1.0	12	0.7	0.4	1.3	20	0.6	0.4	0.9	5	0.3	0.1	0.7
Nervous system disorders (10029205)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	1	0.1	0.0	0.3
Respiratory, thoracic and mediastinal disorders (10038738)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2

N = number of subjects with at least one administered dose
At least one symptom = number of HIV positive subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of HIV positive subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 223 Percentage of subjects with SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	71	4.3	3.4	5.4	62	3.8	2.9	4.8	133	4.0	3.4	4.8	74	4.5	3.6	5.6
Infections and infestations (10021881)	69	4.2	3.3	5.3	62	3.8	2.9	4.8	131	4.0	3.3	4.7	74	4.5	3.6	5.6
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
n (%)= number (percentage) of subjects reporting at least once the specified SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 224 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	170	10.3	8.9	11.9	189	11.5	10.0	13.2	1.20	-0.94	3.34	0.272
Blood and lymphatic system disorders (10005329)	3	0.2	0.0	0.5	4	0.2	0.1	0.6	0.06	-0.32	0.46	0.702
Cardiac disorders (10007541)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
Eye disorders (10015919)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Gastrointestinal disorders (10017947)	6	0.4	0.1	0.8	6	0.4	0.1	0.8	0.00	-0.47	0.47	0.995
General disorders and administration site conditions (10018065)	2	0.1	0.0	0.4	6	0.4	0.1	0.8	0.24	-0.12	0.69	0.155
Immune system disorders (10021428)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	160	9.7	8.3	11.2	171	10.4	9.0	12.0	0.71	-1.36	2.77	0.501
Injury, poisoning and procedural complications (10022117)	3	0.2	0.0	0.5	6	0.4	0.1	0.8	0.18	-0.21	0.63	0.314
Metabolism and nutrition disorders (10027433)	10	0.6	0.3	1.1	12	0.7	0.4	1.3	0.12	-0.47	0.74	0.663
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Nervous system disorders (10029205)	3	0.2	0.0	0.5	10	0.6	0.3	1.1	0.43	-0.00	0.96	0.051
Respiratory, thoracic and mediastinal disorders (10038738)	4	0.2	0.1	0.6	6	0.4	0.1	0.8	0.12	-0.30	0.58	0.523
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Surgical and medical procedures (10042613)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)

P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 225 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	149	9.0	7.7	10.5	189	11.5	10.0	13.2	2.49	0.42	4.58	0.018
Blood and lymphatic system disorders (10005329)	5	0.3	0.1	0.7	4	0.2	0.1	0.6	-0.06	-0.49	0.36	0.745
Cardiac disorders (10007541)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
Gastrointestinal disorders (10017947)	3	0.2	0.0	0.5	6	0.4	0.1	0.8	0.18	-0.21	0.63	0.312
General disorders and administration site conditions (10018065)	7	0.4	0.2	0.9	6	0.4	0.1	0.8	-0.06	-0.55	0.42	0.790
Immune system disorders (10021428)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	135	8.2	6.9	9.6	171	10.4	9.0	12.0	2.24	0.26	4.24	0.027
Injury, poisoning and procedural complications (10022117)	1	0.1	0.0	0.3	6	0.4	0.1	0.8	0.31	-0.01	0.74	0.057
Metabolism and nutrition disorders (10027433)	7	0.4	0.2	0.9	12	0.7	0.4	1.3	0.31	-0.23	0.90	0.245
Nervous system disorders (10029205)	8	0.5	0.2	1.0	10	0.6	0.3	1.1	0.12	-0.42	0.69	0.627
Renal and urinary disorders (10038359)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Respiratory, thoracic and mediastinal disorders (10038738)	6	0.4	0.1	0.8	6	0.4	0.1	0.8	0.00	-0.47	0.48	0.992
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Vascular disorders (10047065)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups

(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 226 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	319	9.7	8.7	10.7	189	11.5	10.0	13.2	1.84	0.05	3.74	0.044
Blood and lymphatic system disorders (10005329)	8	0.2	0.1	0.5	4	0.2	0.1	0.6	0.00	-0.28	0.40	0.994
Cardiac disorders (10007541)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
Congenital, familial and genetic disorders (10010331)	2	0.1	0.0	0.2	1	0.1	0.0	0.3	0.00	-0.17	0.29	0.997
Eye disorders (10015919)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Gastrointestinal disorders (10017947)	9	0.3	0.1	0.5	6	0.4	0.1	0.8	0.09	-0.22	0.54	0.577
General disorders and administration site conditions (10018065)	9	0.3	0.1	0.5	6	0.4	0.1	0.8	0.09	-0.22	0.54	0.577
Immune system disorders (10021428)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Infections and infestations (10021881)	295	8.9	8.0	10.0	171	10.4	9.0	12.0	1.48	-0.25	3.30	0.095
Injury, poisoning and procedural complications (10022117)	4	0.1	0.0	0.3	6	0.4	0.1	0.8	0.24	-0.02	0.68	0.072
Metabolism and nutrition disorders (10027433)	17	0.5	0.3	0.8	12	0.7	0.4	1.3	0.22	-0.22	0.79	0.350
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Nervous system disorders (10029205)	11	0.3	0.2	0.6	10	0.6	0.3	1.1	0.28	-0.10	0.81	0.161
Renal and urinary disorders (10038359)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Respiratory, thoracic and mediastinal disorders (10038738)	10	0.3	0.1	0.6	6	0.4	0.1	0.8	0.06	-0.26	0.51	0.716
Skin and subcutaneous tissue disorders (10040785)	0	0.0	0.0	0.1	2	0.1	0.0	0.4	0.12	0.01	0.44	0.045
Surgical and medical procedures (10042613)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
Vascular disorders (10047065)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 227 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	71	4.3	3.4	5.4	74	4.5	3.6	5.6	0.20	-1.22	1.62	0.782
Infections and infestations (10021881)	69	4.2	3.3	5.3	74	4.5	3.6	5.6	0.32	-1.09	1.73	0.653
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
n (%)= number (percentage) of subjects reporting at least once the specified SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 228 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	62	3.8	2.9	4.8	74	4.5	3.6	5.6	0.75	-0.61	2.14	0.277
Infections and infestations (10021881)	62	3.8	2.9	4.8	74	4.5	3.6	5.6	0.75	-0.61	2.14	0.277

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
n (%)= number (percentage) of subjects reporting at least once the specified SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 229 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with SAEs coded to the various MedDRA preferred terms (PT) catagories for 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	133	4.0	3.4	4.8	74	4.5	3.6	5.6	0.48	-0.68	1.75	0.431
Infections and infestations (10021881)	131	4.0	3.3	4.7	74	4.5	3.6	5.6	0.54	-0.62	1.81	0.373
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
n (%)= number (percentage) of subjects reporting at least once the specified SAEs coded to the various MedDRA preferred terms (PT) categories for 'Pneumonia disease'
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 230 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		170	10.3	8.9	11.9	149	9.0	7.7	10.5	319	9.7	8.7	10.7	189	11.5	10.0	13.2
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	2	0.1	0.0	0.4	4	0.2	0.1	0.6	6	0.2	0.1	0.4	2	0.1	0.0	0.4
	Haemorrhagic disorder (10019009)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Lymphadenitis (10025188)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Pancytopenia (10033661)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Tachycardia (10043071)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Patent ductus arteriosus (10034130)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Eye disorders (10015919)	Blindness (10005169)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Gastrointestinal disorders (10017947)	Abdominal distension (10000060)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Gastrointestinal disorder	2	0.1	0.0	0.4	2	0.1	0.0	0.4	4	0.1	0.0	0.3	2	0.1	0.0	0.4

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10017944)																
	Ileus (10021328)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Ileus paralytic (10021333)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Inguinal hernia (10022016)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Intestinal obstruction (10022687)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Intussusception (10022863)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Vomiting (10047700)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
General disorders and administration site conditions (10018065)	Cyst (10011732)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Death (10011906)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	4	0.1	0.0	0.3	0	0.0	0.0	0.2
	Irritability (10022998)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Pyrexia (10037660)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	2	0.1	0.0	0.4
	Sudden death (10042434)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	2	0.1	0.0	0.4
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Infections and infestations (10021881)	Abscess (10000269)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Abscess neck (10053576)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Acquired	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	immunodeficiency syndrome (10000565)																
	Arthritis bacterial (10053555)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Bronchiolitis (10006448)	18	1.1	0.6	1.7	15	0.9	0.5	1.5	33	1.0	0.7	1.4	16	1.0	0.6	1.6
	Bronchitis (10006451)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	2	0.1	0.0	0.4
	Bronchopneumonia (10006469)	25	1.5	1.0	2.2	21	1.3	0.8	1.9	46	1.4	1.0	1.9	23	1.4	0.9	2.1
	Cellulitis (10007882)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Cerebral malaria (10063094)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Croup infectious (10011416)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	1	0.1	0.0	0.3
	Disseminated tuberculosis (10013453)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Eczema infected (10014199)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Empyema (10014568)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Febrile infection (10051998)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Gastroenteritis (10017888)	76	4.6	3.7	5.7	49	3.0	2.2	3.9	125	3.8	3.2	4.5	79	4.8	3.8	6.0
	Herpes simplex	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10019948)																
	Infection (10021789)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Klebsiella bacteraemia (10058856)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	3	0.2	0.0	0.5
	Malaria (10025487)	12	0.7	0.4	1.3	9	0.5	0.2	1.0	21	0.6	0.4	1.0	19	1.2	0.7	1.8
	Meningitis (10027199)	7	0.4	0.2	0.9	3	0.2	0.0	0.5	10	0.3	0.1	0.6	2	0.1	0.0	0.4
	Meningitis bacterial (10027202)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	2	0.1	0.0	0.4
	Meningitis tuberculous (10027259)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Nosocomial infection (10029803)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Oral candidiasis (10030963)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	3	0.2	0.0	0.5
	Otitis media (10033078)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	1	0.1	0.0	0.3
	Otitis media acute (10033079)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Parotid abscess (10034019)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Perianal abscess	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10034447)																
	Pharyngotonsillitis (10049140)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Pneumocystis jiroveci pneumonia (10064108)	4	0.2	0.1	0.6	4	0.2	0.1	0.6	8	0.2	0.1	0.5	4	0.2	0.1	0.6
	Pneumonia (10035664)	40	2.4	1.7	3.3	36	2.2	1.5	3.0	76	2.3	1.8	2.9	46	2.8	2.1	3.7
	Pneumonia bacterial (10060946)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Pneumonia viral (10035737)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	2	0.1	0.0	0.4
	Postoperative wound infection (10036410)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Pulmonary tuberculosis (10037440)	3	0.2	0.0	0.5	3	0.2	0.0	0.5	6	0.2	0.1	0.4	2	0.1	0.0	0.4
	Respiratory tract infection (10062352)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Respiratory tract infection viral (10062106)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Sepsis (10040047)	25	1.5	1.0	2.2	22	1.3	0.8	2.0	47	1.4	1.0	1.9	19	1.2	0.7	1.8
	Sepsis neonatal (10040049)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Septic shock (10040070)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Staphylococcal skin infection	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10066409)																
	Subcutaneous abscess (10042343)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	2	0.1	0.0	0.4
	Tonsillitis (10044008)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Tuberculosis (10044755)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Upper respiratory tract infection (10046306)	6	0.4	0.1	0.8	6	0.4	0.1	0.8	12	0.4	0.2	0.6	1	0.1	0.0	0.3
	Urinary tract infection (10046571)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	2	0.1	0.0	0.4
	Varicella (10046980)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Viral tonsillitis (10047480)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Viral upper respiratory tract infection (10047482)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Injury, poisoning and procedural complications (10022117)	Brachial plexus injury (10006074)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Femur fracture (10016454)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Fractured skull depressed (10017310)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Head injury (10019196)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Injury (10022116)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Pneumonitis chemical (10035745)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Soft tissue injury (10041291)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Thermal burn (10053615)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Dehydration (10012174)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	5	0.2	0.0	0.4	2	0.1	0.0	0.4
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Hypernatraemia (10020679)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	2	0.1	0.0	0.4
	Hypoglycaemic seizure (10048803)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Hypokalaemia (10021015)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Hyponatraemic syndrome (10021037)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Kwashiorkor (10023504)	3	0.2	0.0	0.5	1	0.1	0.0	0.3	4	0.1	0.0	0.3	4	0.2	0.1	0.6
	Malnutrition (10061273)	5	0.3	0.1	0.7	0	0.0	0.0	0.2	5	0.2	0.0	0.4	0	0.0	0.0	0.2
	Marasmus (10026820)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	3	0.2	0.0	0.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Neuroblastoma (10029260)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Encephalitis (10014581)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	2	0.1	0.0	0.4
	Febrile convulsion (10016284)	1	0.1	0.0	0.3	5	0.3	0.1	0.7	6	0.2	0.1	0.4	5	0.3	0.1	0.7
	Fontanelle bulging (10016945)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Hydrocephalus (10020508)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	2	0.1	0.0	0.4
	Status epilepticus (10041962)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2
Renal and urinary disorders (10038359)	Renal failure (10038435)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Aspiration (10003504)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Asthma (10003553)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	2	0.1	0.0	0.4
	Atelectasis (10003598)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Bronchospasm (10006482)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Dyspnoea (10013968)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Epistaxis (10015090)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Grunting (10018762)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Pneumothorax (10035759)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Respiratory arrest (10038669)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Respiratory distress (10038687)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Respiratory failure (10038695)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Urticaria (10046735)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Surgical and medical procedures (10042613)	Adenoidectomy (10001230)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Vascular disorders (10047065)	Hypovolaemic shock (10021138)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 231 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 1)

		HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		53	8.7	6.6	11.2	38	6.2	4.4	8.4	91	7.4	6.0	9.1	62	10.2	7.9	12.9
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	0	0.0	0.0	0.6
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Tachycardia (10043071)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Patent ductus arteriosus (10034130)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
Eye disorders (10015919)	Blindness (10005169)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Gastrointestinal disorders (10017947)	Abdominal distension (10000060)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Inguinal hernia (10022016)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Vomiting (10047700)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
General disorders and administration site conditions (10018065)	Cyst (10011732)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Death (10011906)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6

		HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pyrexia (10037660)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	0.9
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	2	0.3	0.0	1.2
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Bronchiolitis (10006448)	6	1.0	0.4	2.1	3	0.5	0.1	1.4	9	0.7	0.3	1.4	6	1.0	0.4	2.1
	Bronchitis (10006451)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	2	0.3	0.0	1.2
	Bronchopneumonia (10006469)	16	2.6	1.5	4.2	12	2.0	1.0	3.4	28	2.3	1.5	3.3	8	1.3	0.6	2.6
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Gastroenteritis (10017888)	23	3.8	2.4	5.6	16	2.6	1.5	4.2	39	3.2	2.3	4.3	33	5.5	3.8	7.6
	Herpes simplex (10019948)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Klebsiella bacteraemia (10058856)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Meningitis (10027199)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.2	0.1	0.7	1	0.2	0.0	0.9
	Meningitis bacterial (10027202)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Meningitis	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

		HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	tuberculous (10027259)																
	Otitis media (10033078)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Perianal abscess (10034447)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Pharyngotonsillitis (10049140)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Pneumocystis jiroveci pneumonia (10064108)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.2	0.1	0.7	2	0.3	0.0	1.2
	Pneumonia (10035664)	5	0.8	0.3	1.9	1	0.2	0.0	0.9	6	0.5	0.2	1.1	4	0.7	0.2	1.7
	Pneumonia viral (10035737)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Respiratory tract infection (10062352)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Sepsis (10040047)	1	0.2	0.0	0.9	4	0.7	0.2	1.7	5	0.4	0.1	1.0	1	0.2	0.0	0.9
	Tonsillitis (10044008)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Upper respiratory tract infection (10046306)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Viral tonsillitis (10047480)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Injury, poisoning and procedural complications (10022117)	Brachial plexus injury (10006074)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Femur fracture (10016454)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Head injury	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6

		HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10019196)																
	Pneumonitis chemical (10035745)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Thermal burn (10053615)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	0.9
Metabolism and nutrition disorders (10027433)	Dehydration (10012174)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.2	0.1	0.7	1	0.2	0.0	0.9
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Hypernatraemia (10020679)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Hypoglycaemic seizure (10048803)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Hypokalaemia (10021015)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Hyponatraemic syndrome (10021037)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Kwashiorkor (10023504)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Malnutrition (10061273)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	0	0.0	0.0	0.6
	Metabolic acidosis (10027417)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	2	0.3	0.0	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Neuroblastoma (10029260)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6

		HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Encephalitis (10014581)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Febrile convulsion (10016284)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Hydrocephalus (10020508)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
Renal and urinary disorders (10038359)	Renal failure (10038435)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	2	0.3	0.0	1.2
	Atelectasis (10003598)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Bronchospasm (10006482)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Dyspnoea (10013968)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Epistaxis (10015090)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Grunting (10018762)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Pneumonia aspiration (10035669)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Respiratory failure (10038695)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)

n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 232 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 2 South Africa)

		HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		29	6.5	4.4	9.2	29	6.5	4.4	9.2	58	6.5	5.0	8.3	34	7.6	5.3	10.5
Blood and lymphatic system disorders (10005329)	Lymphadenitis (10025188)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Pancytopenia (10033661)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Gastrointestinal disorders (10017947)	Gastrointestinal disorder (10017944)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	2	0.4	0.1	1.6
	Ileus (10021328)	1	0.2	0.0	1.2	0	0.0	0.0	0.8	1	0.1	0.0	0.6	0	0.0	0.0	0.8
General disorders and administration site conditions (10018065)	Irritability (10022998)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Sudden death (10042434)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Infections and infestations (10021881)	Bronchiolitis (10006448)	5	1.1	0.4	2.6	4	0.9	0.2	2.3	9	1.0	0.5	1.9	5	1.1	0.4	2.6
	Bronchopneumonia (10006469)	9	2.0	0.9	3.8	9	2.0	0.9	3.8	18	2.0	1.2	3.2	15	3.4	1.9	5.5
	Cellulitis	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2

		HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10007882)																
	Croup infectious (10011416)	1	0.2	0.0	1.2	1	0.2	0.0	1.2	2	0.2	0.0	0.8	0	0.0	0.0	0.8
	Disseminated tuberculosis (10013453)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Gastroenteritis (10017888)	13	2.9	1.6	4.9	11	2.5	1.2	4.4	24	2.7	1.7	4.0	16	3.6	2.1	5.8
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	2	0.4	0.1	1.6
	Meningitis (10027199)	3	0.7	0.1	1.9	0	0.0	0.0	0.8	3	0.3	0.1	1.0	0	0.0	0.0	0.8
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Nosocomial infection (10029803)	1	0.2	0.0	1.2	0	0.0	0.0	0.8	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Otitis media (10033078)	1	0.2	0.0	1.2	1	0.2	0.0	1.2	2	0.2	0.0	0.8	0	0.0	0.0	0.8
	Otitis media acute (10033079)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Pneumocystis jiroveci pneumonia (10064108)	1	0.2	0.0	1.2	2	0.4	0.1	1.6	3	0.3	0.1	1.0	0	0.0	0.0	0.8
	Pneumonia (10035664)	3	0.7	0.1	1.9	3	0.7	0.1	1.9	6	0.7	0.2	1.5	2	0.4	0.1	1.6
	Pulmonary tuberculosis (10037440)	1	0.2	0.0	1.2	1	0.2	0.0	1.2	2	0.2	0.0	0.8	2	0.4	0.1	1.6
	Sepsis (10040047)	2	0.4	0.1	1.6	0	0.0	0.0	0.8	2	0.2	0.0	0.8	1	0.2	0.0	1.2

		HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Subcutaneous abscess (10042343)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Tonsillitis (10044008)	1	0.2	0.0	1.2	0	0.0	0.0	0.8	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Upper respiratory tract infection (10046306)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Urinary tract infection (10046571)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	1	0.2	0.0	1.2
Metabolism and nutrition disorders (10027433)	Dehydration (10012174)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Hypernatraemia (10020679)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Kwashiorkor (10023504)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	2	0.4	0.1	1.6
	Marasmus (10026820)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Metabolic acidosis (10027417)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
	Encephalitis (10014581)	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.4	1	0.2	0.0	1.2
	Febrile convulsion (10016284)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	2	0.4	0.1	1.6
	Fontanelle bulging (10016945)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	1	0.2	0.0	1.2
	Status epilepticus (10041962)	1	0.2	0.0	1.2	0	0.0	0.0	0.8	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Respiratory, thoracic and	Aspiration	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8

		HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
mediastinal disorders (10038738)	(10003504)																
	Asthma (10003553)	1	0.2	0.0	1.2	1	0.2	0.0	1.2	2	0.2	0.0	0.8	0	0.0	0.0	0.8
	Respiratory arrest (10038669)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Surgical and medical procedures (10042613)	Adenoidectomy (10001230)	1	0.2	0.0	1.2	0	0.0	0.0	0.8	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Vascular disorders (10047065)	Hypovolaemic shock (10021138)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 233 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, South Africa)

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		82	7.8	6.2	9.5	67	6.3	4.9	8.0	149	7.0	6.0	8.2	96	9.1	7.5	11.1
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	2	0.2	0.0	0.7	0	0.0	0.0	0.3	2	0.1	0.0	0.3	0	0.0	0.0	0.4
	Lymphadenitis (10025188)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Pancytopenia (10033661)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Tachycardia (10043071)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Patent ductus arteriosus (10034130)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
Eye disorders (10015919)	Blindness (10005169)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Gastrointestinal disorders (10017947)	Abdominal distension (10000060)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Gastrointestinal disorder (10017944)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	2	0.2	0.0	0.7
	Ileus (10021328)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Inguinal hernia (10022016)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Vomiting (10047700)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
General disorders and administration site conditions (10018065)	Cyst (10011732)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Death (10011906)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Irritability (10022998)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Pyrexia (10037660)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	1	0.1	0.0	0.5
	Sudden death (10042434)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.3	2	0.2	0.0	0.7	2	0.1	0.0	0.3	2	0.2	0.0	0.7
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Bronchiolitis (10006448)	11	1.0	0.5	1.9	7	0.7	0.3	1.4	18	0.9	0.5	1.3	11	1.0	0.5	1.9
	Bronchitis (10006451)	2	0.2	0.0	0.7	0	0.0	0.0	0.3	2	0.1	0.0	0.3	2	0.2	0.0	0.7
	Bronchopneumonia (10006469)	25	2.4	1.5	3.5	21	2.0	1.2	3.0	46	2.2	1.6	2.9	23	2.2	1.4	3.3
	Cellulitis (10007882)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Croup infectious (10011416)	1	0.1	0.0	0.5	1	0.1	0.0	0.5	2	0.1	0.0	0.3	0	0.0	0.0	0.4
	Disseminated tuberculosis	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10013453)																
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Gastroenteritis (10017888)	36	3.4	2.4	4.7	27	2.5	1.7	3.7	63	3.0	2.3	3.8	49	4.7	3.5	6.1
	Herpes simplex (10019948)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Klebsiella bacteraemia (10058856)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	2	0.2	0.0	0.7
	Meningitis (10027199)	5	0.5	0.2	1.1	1	0.1	0.0	0.5	6	0.3	0.1	0.6	1	0.1	0.0	0.5
	Meningitis bacterial (10027202)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	1	0.1	0.0	0.5
	Meningitis tuberculous (10027259)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Nosocomial infection (10029803)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Otitis media (10033078)	1	0.1	0.0	0.5	1	0.1	0.0	0.5	2	0.1	0.0	0.3	1	0.1	0.0	0.5
	Otitis media acute (10033079)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Perianal abscess	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10034447)																
	Pharyngotonsillitis (10049140)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Pneumocystis jiroveci pneumonia (10064108)	3	0.3	0.1	0.8	3	0.3	0.1	0.8	6	0.3	0.1	0.6	2	0.2	0.0	0.7
	Pneumonia (10035664)	8	0.8	0.3	1.5	4	0.4	0.1	1.0	12	0.6	0.3	1.0	6	0.6	0.2	1.2
	Pneumonia viral (10035737)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Pulmonary tuberculosis (10037440)	1	0.1	0.0	0.5	1	0.1	0.0	0.5	2	0.1	0.0	0.3	2	0.2	0.0	0.7
	Respiratory tract infection (10062352)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Sepsis (10040047)	3	0.3	0.1	0.8	4	0.4	0.1	1.0	7	0.3	0.1	0.7	2	0.2	0.0	0.7
	Subcutaneous abscess (10042343)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Tonsillitis (10044008)	2	0.2	0.0	0.7	0	0.0	0.0	0.3	2	0.1	0.0	0.3	0	0.0	0.0	0.4
	Upper respiratory tract infection (10046306)	0	0.0	0.0	0.3	2	0.2	0.0	0.7	2	0.1	0.0	0.3	0	0.0	0.0	0.4
	Urinary tract infection (10046571)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	1	0.1	0.0	0.5
	Viral tonsillitis (10047480)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Injury, poisoning and procedural complications	Brachial plexus injury (10006074)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
(10022117)																	
	Femur fracture (10016454)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Head injury (10019196)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Pneumonitis chemical (10035745)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Thermal burn (10053615)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	1	0.1	0.0	0.5
Metabolism and nutrition disorders (10027433)	Dehydration (10012174)	2	0.2	0.0	0.7	2	0.2	0.0	0.7	4	0.2	0.1	0.5	1	0.1	0.0	0.5
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Hypernatraemia (10020679)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	2	0.2	0.0	0.7
	Hypoglycaemic seizure (10048803)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Hypokalaemia (10021015)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Hyponatraemic syndrome (10021037)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Kwashiorkor (10023504)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	2	0.2	0.0	0.7
	Malnutrition (10061273)	2	0.2	0.0	0.7	0	0.0	0.0	0.3	2	0.1	0.0	0.3	0	0.0	0.0	0.4
	Marasmus (10026820)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Metabolic acidosis (10027417)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	3	0.3	0.1	0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Neuroblastoma (10029260)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	1	0.1	0.0	0.5
	Encephalitis (10014581)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	2	0.2	0.0	0.7
	Febrile convulsion (10016284)	0	0.0	0.0	0.3	2	0.2	0.0	0.7	2	0.1	0.0	0.3	2	0.2	0.0	0.7
	Fontanelle bulging (10016945)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	1	0.1	0.0	0.5
	Hydrocephalus (10020508)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Status epilepticus (10041962)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Renal and urinary disorders (10038359)	Renal failure (10038435)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Respiratory, thoracic and mediastinal disorders (10038738)	Aspiration (10003504)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Asthma (10003553)	1	0.1	0.0	0.5	1	0.1	0.0	0.5	2	0.1	0.0	0.3	2	0.2	0.0	0.7
	Atelectasis (10003598)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Bronchospasm (10006482)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Dyspnoea (10013968)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Epistaxis (10015090)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Grunting (10018762)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
	Pneumonia aspiration (10035669)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Respiratory arrest (10038669)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Respiratory failure (10038695)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.2	1	0.1	0.0	0.5
Surgical and medical procedures (10042613)	Adenoidectomy (10001230)	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.0	0.0	0.3	0	0.0	0.0	0.4
Vascular disorders (10047065)	Hypovolaemic shock (10021138)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 234 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Malawi)

		HRV_2D N = 590				HRV_3D N = 592				HRV_POOL N = 1182				Placebo N = 591			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		88	14.9	12.1	18.0	82	13.9	11.2	16.9	170	14.4	12.4	16.5	93	15.7	12.9	18.9
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	0	0.0	0.0	0.6	4	0.7	0.2	1.7	4	0.3	0.1	0.9	2	0.3	0.0	1.2
	Haemorrhagic disorder (10019009)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Lymphadenitis (10025188)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Gastrointestinal disorders (10017947)	Gastrointestinal disorder (10017944)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.3	0.1	0.7	0	0.0	0.0	0.6
	Ileus paralytic (10021333)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	0	0.0	0.0	0.6
	Inguinal hernia (10022016)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Intestinal obstruction (10022687)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Intussusception (10022863)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
General disorders and administration site conditions (10018065)	Death (10011906)	1	0.2	0.0	0.9	2	0.3	0.0	1.2	3	0.3	0.1	0.7	0	0.0	0.0	0.6
	Pyrexia (10037660)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	0.9
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

		HRV_2D N = 590				HRV_3D N = 592				HRV_POOL N = 1182				Placebo N = 591			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Infections and infestations (10021881)	Abscess (10000269)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Abscess neck (10053576)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Arthritis bacterial (10053555)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	2	0.2	0.0	0.6	0	0.0	0.0	0.6
	Bronchiolitis (10006448)	7	1.2	0.5	2.4	8	1.4	0.6	2.6	15	1.3	0.7	2.1	5	0.8	0.3	2.0
	Cerebral malaria (10063094)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Croup infectious (10011416)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Eczema infected (10014199)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Empyema (10014568)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Febrile infection (10051998)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Gastroenteritis (10017888)	40	6.8	4.9	9.1	22	3.7	2.3	5.6	62	5.2	4.0	6.7	30	5.1	3.5	7.2
	Infection (10021789)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	0.9
	Malaria (10025487)	12	2.0	1.1	3.5	9	1.5	0.7	2.9	21	1.8	1.1	2.7	19	3.2	1.9	5.0
	Meningitis (10027199)	2	0.3	0.0	1.2	2	0.3	0.0	1.2	4	0.3	0.1	0.9	1	0.2	0.0	0.9

		HRV_2D N = 590				HRV_3D N = 592				HRV_POOL N = 1182				Placebo N = 591			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Oral candidiasis (10030963)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	3	0.5	0.1	1.5
	Otitis media acute (10033079)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Parotid abscess (10034019)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Pneumocystis jiroveci pneumonia (10064108)	1	0.2	0.0	0.9	1	0.2	0.0	0.9	2	0.2	0.0	0.6	2	0.3	0.0	1.2
	Pneumonia (10035664)	32	5.4	3.7	7.6	32	5.4	3.7	7.5	64	5.4	4.2	6.9	40	6.8	4.9	9.1
	Pneumonia bacterial (10060946)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Pneumonia viral (10035737)	2	0.3	0.0	1.2	0	0.0	0.0	0.6	2	0.2	0.0	0.6	1	0.2	0.0	0.9
	Postoperative wound infection (10036410)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Pulmonary tuberculosis (10037440)	2	0.3	0.0	1.2	2	0.3	0.0	1.2	4	0.3	0.1	0.9	0	0.0	0.0	0.6
	Respiratory tract infection (10062352)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Respiratory tract infection viral (10062106)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Sepsis (10040047)	22	3.7	2.4	5.6	18	3.0	1.8	4.8	40	3.4	2.4	4.6	17	2.9	1.7	4.6

		HRV_2D N = 590				HRV_3D N = 592				HRV_POOL N = 1182				Placebo N = 591			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Sepsis neonatal (10040049)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Septic shock (10040070)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Staphylococcal skin infection (10066409)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	0.9
	Subcutaneous abscess (10042343)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	1	0.2	0.0	0.9
	Tuberculosis (10044755)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Upper respiratory tract infection (10046306)	6	1.0	0.4	2.2	4	0.7	0.2	1.7	10	0.8	0.4	1.6	1	0.2	0.0	0.9
	Urinary tract infection (10046571)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Varicella (10046980)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Viral upper respiratory tract infection (10047482)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Injury, poisoning and procedural complications (10022117)	Fractured skull depressed (10017310)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Injury (10022116)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Soft tissue injury (10041291)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

		HRV_2D N = 590				HRV_3D N = 592				HRV_POOL N = 1182				Placebo N = 591			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Dehydration (10012174)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	1	0.2	0.0	0.9
	Kwashiorkor (10023504)	2	0.3	0.0	1.2	1	0.2	0.0	0.9	3	0.3	0.1	0.7	2	0.3	0.0	1.2
	Malnutrition (10061273)	3	0.5	0.1	1.5	0	0.0	0.0	0.6	3	0.3	0.1	0.7	0	0.0	0.0	0.6
	Marasmus (10026820)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	1	0.2	0.0	0.9
Nervous system disorders (10029205)	Encephalitis (10014581)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Febrile convulsion (10016284)	1	0.2	0.0	0.9	3	0.5	0.1	1.5	4	0.3	0.1	0.9	3	0.5	0.1	1.5
	Hydrocephalus (10020508)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Status epilepticus (10041962)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	0	0.0	0.0	0.6	1	0.2	0.0	0.9	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Pneumonia aspiration (10035669)	1	0.2	0.0	0.9	0	0.0	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.6
	Pneumothorax (10035759)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
	Respiratory distress (10038687)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9
Skin and subcutaneous tissue disorders (10040785)	Urticaria (10046735)	0	0.0	0.0	0.6	0	0.0	0.0	0.6	0	0.0	0.0	0.3	1	0.2	0.0	0.9

At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 235 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		170	10.3	8.9	11.9	189	11.5	10.0	13.2	1.20	-0.94	3.34	0.272
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.997
	Haemorrhagic disorder (10019009)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Lymphadenitis (10025188)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
Cardiac disorders (10007541)	Tachycardia (10043071)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Patent ductus arteriosus (10034130)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Eye disorders (10015919)	Blindness (10005169)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Gastrointestinal disorders (10017947)	Abdominal distension (10000060)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Gastrointestinal disorder (10017944)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.997
	Ileus (10021328)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Ileus paralytic (10021333)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Inguinal hernia (10022016)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
	Intestinal obstruction (10022687)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Vomiting (10047700)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	Death (10011906)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Irritability (10022998)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Pyrexia (10037660)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Sudden death (10042434)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	Abscess neck (10053576)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Arthritis bacterial (10053555)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Bronchiolitis (10006448)	18	1.1	0.6	1.7	16	1.0	0.6	1.6	-0.12	-0.85	0.60	0.738
	Bronchitis (10006451)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.997
	Bronchopneumonia (10006469)	25	1.5	1.0	2.2	23	1.4	0.9	2.1	-0.12	-0.97	0.73	0.781
	Cellulitis (10007882)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Cerebral malaria (10063094)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Croup infectious (10011416)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
	Disseminated tuberculosis (10013453)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Eczema infected (10014199)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Empyema (10014568)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Gastroenteritis (10017888)	76	4.6	3.7	5.7	79	4.8	3.8	6.0	0.20	-1.26	1.67	0.787
	Herpes simplex (10019948)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Infection (10021789)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	0.18	-0.05	0.54	0.083
	Malaria (10025487)	12	0.7	0.4	1.3	19	1.2	0.7	1.8	0.43	-0.25	1.15	0.203

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Meningitis (10027199)	7	0.4	0.2	0.9	2	0.1	0.0	0.4	-0.30	-0.77	0.07	0.096
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Meningitis tuberculous (10027259)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Nosocomial infection (10029803)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Oral candidiasis (10030963)	2	0.1	0.0	0.4	3	0.2	0.0	0.5	0.06	-0.28	0.43	0.652
	Otitis media (10033078)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
	Otitis media acute (10033079)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Parotid abscess (10034019)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Perianal abscess (10034447)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pharyngotonsillitis (10049140)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Pneumocystis jiroveci pneumonia (10064108)	4	0.2	0.1	0.6	4	0.2	0.1	0.6	0.00	-0.41	0.41	0.996
	Pneumonia (10035664)	40	2.4	1.7	3.3	46	2.8	2.1	3.7	0.37	-0.73	1.49	0.501
	Pneumonia viral (10035737)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.997
	Pulmonary tuberculosis (10037440)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.43	0.28	0.657
	Respiratory tract infection (10062352)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
	Respiratory tract infection viral (10062106)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Sepsis (10040047)	25	1.5	1.0	2.2	19	1.2	0.7	1.8	-0.36	-1.19	0.44	0.369
	Staphylococcal skin infection (10066409)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Subcutaneous abscess (10042343)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.561
	Tonsillitis (10044008)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Tuberculosis (10044755)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Upper respiratory tract infection (10046306)	6	0.4	0.1	0.8	1	0.1	0.0	0.3	-0.30	-0.74	0.02	0.059
	Urinary tract infection (10046571)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Varicella (10046980)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Viral tonsillitis (10047480)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Viral upper respiratory tract infection (10047482)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Injury, poisoning and procedural complications (10022117)	Brachial plexus injury (10006074)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Femur fracture (10016454)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Fractured skull depressed (10017310)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Head injury (10019196)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Injury (10022116)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pneumonitis chemical (10035745)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Soft tissue injury (10041291)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Thermal burn (10053615)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Dehydration (10012174)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.43	0.28	0.657
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Hypernatraemia (10020679)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Hypoglycaemic seizure (10048803)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Kwashiorkor (10023504)	3	0.2	0.0	0.5	4	0.2	0.1	0.6	0.06	-0.32	0.46	0.702
	Malnutrition (10061273)	5	0.3	0.1	0.7	0	0.0	0.0	0.2	-0.30	-0.71	-0.07	0.026

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Marasmus (10026820)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	0.18	-0.05	0.54	0.083
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Neuroblastoma (10029260)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Encephalitis (10014581)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.561
	Febrile convulsion (10016284)	1	0.1	0.0	0.3	5	0.3	0.1	0.7	0.24	-0.07	0.66	0.101
	Fontanelle bulging (10016945)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Hydrocephalus (10020508)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Status epilepticus (10041962)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Respiratory, thoracic and mediastinal disorders (10038738)	Asthma (10003553)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.561
	Atelectasis (10003598)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Dyspnoea (10013968)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Epistaxis (10015090)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Grunting (10018762)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Pneumothorax (10035759)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Respiratory distress (10038687)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Urticaria (10046735)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Surgical and medical procedures (10042613)	Adenoidectomy (10001230)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)

n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 236 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		149	9.0	7.7	10.5	189	11.5	10.0	13.2	2.49	0.42	4.58	0.018
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	4	0.2	0.1	0.6	2	0.1	0.0	0.4	-0.12	-0.51	0.23	0.418
	Haemorrhagic disorder (10019009)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Lymphadenitis (10025188)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pancytopenia (10033661)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Patent ductus arteriosus (10034130)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Gastrointestinal disorders (10017947)	Abdominal distension (10000060)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Gastrointestinal disorder	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.995

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	(10017944)												
	Inguinal hernia (10022016)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Intestinal obstruction (10022687)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Intussusception (10022863)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Vomiting (10047700)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	Cyst (10011732)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Death (10011906)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Irritability (10022998)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pyrexia (10037660)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.995
	Sudden death (10042434)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sudden infant death syndrome (10042440)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.995
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	Abscess (10000269)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Acquired immunodeficiency syndrome (10000565)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Arthritis bacterial (10053555)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Bronchiolitis (10006448)	15	0.9	0.5	1.5	16	1.0	0.6	1.6	0.07	-0.63	0.77	0.843
	Bronchitis (10006451)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Bronchopneumonia (10006469)	21	1.3	0.8	1.9	23	1.4	0.9	2.1	0.13	-0.68	0.95	0.746
	Cellulitis (10007882)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Croup infectious (10011416)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Disseminated tuberculosis (10013453)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Empyema (10014568)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Escherichia urinary tract infection (10052238)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Febrile infection (10051998)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Gastroenteritis (10017888)	49	3.0	2.2	3.9	79	4.8	3.8	6.0	1.85	0.53	3.20	0.006
	Infection (10021789)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Klebsiella bacteraemia (10058856)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Lower respiratory tract infection (10024968)	2	0.1	0.0	0.4	3	0.2	0.0	0.5	0.06	-0.28	0.43	0.650
	Malaria (10025487)	9	0.5	0.2	1.0	19	1.2	0.7	1.8	0.61	-0.02	1.31	0.056
	Meningitis (10027199)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.42	0.28	0.659
	Meningitis bacterial (10027202)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Meningitis pneumococcal (10027253)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.560
	Meningitis tuberculous (10027259)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Oral candidiasis (10030963)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	0.18	-0.05	0.54	0.082
	Otitis media (10033078)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Otitis media acute (10033079)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Perianal abscess (10034447)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pneumocystis jiroveci pneumonia (10064108)	4	0.2	0.1	0.6	4	0.2	0.1	0.6	0.00	-0.41	0.41	0.993
	Pneumonia (10035664)	36	2.2	1.5	3.0	46	2.8	2.1	3.7	0.62	-0.45	1.72	0.252
	Pneumonia bacterial (10060946)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Pneumonia viral (10035737)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Postoperative wound infection (10036410)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Pulmonary tuberculosis (10037440)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.42	0.28	0.659

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Respiratory tract infection (10062352)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sepsis (10040047)	22	1.3	0.8	2.0	19	1.2	0.7	1.8	-0.17	-0.97	0.61	0.651
	Sepsis neonatal (10040049)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Septic shock (10040070)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Staphylococcal skin infection (10066409)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Subcutaneous abscess (10042343)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Upper respiratory tract infection (10046306)	6	0.4	0.1	0.8	1	0.1	0.0	0.3	-0.30	-0.74	0.02	0.060
	Urinary tract infection (10046571)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.560
Injury, poisoning and procedural complications (10022117)	Femur fracture (10016454)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Injury (10022116)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pneumonitis chemical (10035745)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Soft tissue injury (10041291)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Thermal burn (10053615)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Dehydration (10012174)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.995
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Hypernatraemia (10020679)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Hypoglycaemic seizure (10048803)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Hypokalaemia (10021015)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Hyponatraemic syndrome (10021037)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Kwashiorkor (10023504)	1	0.1	0.0	0.3	4	0.2	0.1	0.6	0.18	-0.12	0.57	0.177
	Marasmus (10026820)	2	0.1	0.0	0.4	1	0.1	0.0	0.3	-0.06	-0.39	0.23	0.567
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	0.18	-0.05	0.54	0.082
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Encephalitis (10014581)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Febrile convulsion (10016284)	5	0.3	0.1	0.7	5	0.3	0.1	0.7	0.00	-0.44	0.44	0.992
	Fontanelle bulging (10016945)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Hydrocephalus (10020508)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Status epilepticus (10041962)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Renal and urinary disorders (10038359)	Renal failure (10038435)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Aspiration (10003504)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Asthma (10003553)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.560
	Atelectasis (10003598)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Bronchospasm (10006482)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Dyspnoea (10013968)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Grunting (10018762)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pneumothorax (10035759)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Respiratory arrest (10038669)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Respiratory distress (10038687)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Respiratory failure (10038695)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Urticaria (10046735)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Vascular disorders (10047065)	Hypovolaemic shock (10021138)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 237 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		319	9.7	8.7	10.7	189	11.5	10.0	13.2	1.84	0.05	3.74	0.044
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	6	0.2	0.1	0.4	2	0.1	0.0	0.4	-0.06	-0.30	0.27	0.621
	Haemorrhagic disorder (10019009)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Lymphadenitis (10025188)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Pancytopenia (10033661)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Tachycardia (10043071)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Patent ductus arteriosus (10034130)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Eye disorders (10015919)	Blindness (10005169)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Gastrointestinal disorders (10017947)	Abdominal distension (10000060)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Gastrointestinal disorder (10017944)	4	0.1	0.0	0.3	2	0.1	0.0	0.4	0.00	-0.21	0.33	0.996
	Ileus (10021328)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Ileus paralytic (10021333)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Inguinal hernia (10022016)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Intestinal obstruction (10022687)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Intussusception (10022863)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Vomiting (10047700)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
General disorders and administration site conditions (10018065)	Cyst (10011732)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Death (10011906)	4	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.12	-0.31	0.11	0.158
	Irritability (10022998)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Pyrexia (10037660)	2	0.1	0.0	0.2	2	0.1	0.0	0.4	0.06	-0.12	0.39	0.476
	Sudden death (10042434)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Sudden infant death syndrome (10042440)	2	0.1	0.0	0.2	2	0.1	0.0	0.4	0.06	-0.12	0.39	0.476
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Infections and infestations (10021881)	Abscess (10000269)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Abscess neck (10053576)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Acquired immunodeficiency syndrome (10000565)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Arthritis bacterial (10053555)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Bronchiolitis (10006448)	33	1.0	0.7	1.4	16	1.0	0.6	1.6	-0.03	-0.58	0.64	0.932
	Bronchitis (10006451)	2	0.1	0.0	0.2	2	0.1	0.0	0.4	0.06	-0.12	0.39	0.476
	Bronchopneumonia (10006469)	46	1.4	1.0	1.9	23	1.4	0.9	2.1	0.01	-0.65	0.78	0.985
	Cellulitis (10007882)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Cerebral malaria (10063094)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Croup infectious (10011416)	2	0.1	0.0	0.2	1	0.1	0.0	0.3	0.00	-0.17	0.29	0.997
	Disseminated tuberculosis (10013453)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Eczema infected (10014199)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Empyema (10014568)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Escherichia urinary tract	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	infection (10052238)												
	Febrile infection (10051998)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Gastroenteritis (10017888)	125	3.8	3.2	4.5	79	4.8	3.8	6.0	1.02	-0.15	2.32	0.088
	Herpes simplex (10019948)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Infection (10021789)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Klebsiella bacteraemia (10058856)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Lower respiratory tract infection (10024968)	2	0.1	0.0	0.2	3	0.2	0.0	0.5	0.12	-0.07	0.48	0.203
	Malaria (10025487)	21	0.6	0.4	1.0	19	1.2	0.7	1.8	0.52	-0.01	1.20	0.054
	Meningitis (10027199)	10	0.3	0.1	0.6	2	0.1	0.0	0.4	-0.18	-0.46	0.16	0.223
	Meningitis bacterial (10027202)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Meningitis pneumococcal (10027253)	1	0.0	0.0	0.2	2	0.1	0.0	0.4	0.09	-0.07	0.41	0.219
	Meningitis tuberculous (10027259)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Nosocomial infection (10029803)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Oral candidiasis (10030963)	2	0.1	0.0	0.2	3	0.2	0.0	0.5	0.12	-0.07	0.48	0.203
	Otitis media (10033078)	2	0.1	0.0	0.2	1	0.1	0.0	0.3	0.00	-0.17	0.29	0.997
	Otitis media acute (10033079)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Parotid abscess (10034019)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Perianal abscess (10034447)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Pharyngotonsillitis (10049140)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Pneumocystis jiroveci pneumonia (10064108)	8	0.2	0.1	0.5	4	0.2	0.1	0.6	0.00	-0.28	0.40	0.994
	Pneumonia (10035664)	76	2.3	1.8	2.9	46	2.8	2.1	3.7	0.50	-0.40	1.52	0.287
	Pneumonia bacterial (10060946)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Pneumonia viral (10035737)	2	0.1	0.0	0.2	2	0.1	0.0	0.4	0.06	-0.12	0.39	0.476
	Postoperative wound infection (10036410)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Pulmonary tuberculosis (10037440)	6	0.2	0.1	0.4	2	0.1	0.0	0.4	-0.06	-0.30	0.27	0.621
	Respiratory tract infection (10062352)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Respiratory tract infection viral (10062106)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Sepsis (10040047)	47	1.4	1.0	1.9	19	1.2	0.7	1.8	-0.27	-0.90	0.46	0.441
	Sepsis neonatal (10040049)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Septic shock (10040070)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Staphylococcal skin infection (10066409)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Subcutaneous abscess (10042343)	1	0.0	0.0	0.2	2	0.1	0.0	0.4	0.09	-0.07	0.41	0.219
	Tonsillitis (10044008)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Tuberculosis (10044755)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Upper respiratory tract infection (10046306)	12	0.4	0.2	0.6	1	0.1	0.0	0.3	-0.30	-0.58	0.00	0.050
	Urinary tract infection (10046571)	1	0.0	0.0	0.2	2	0.1	0.0	0.4	0.09	-0.07	0.41	0.219
	Varicella (10046980)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Viral tonsillitis (10047480)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Viral upper respiratory tract infection (10047482)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Injury, poisoning and procedural complications (10022117)	Brachial plexus injury (10006074)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Femur fracture (10016454)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Fractured skull depressed	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	(10017310)												
	Head injury (10019196)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Injury (10022116)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Pneumonitis chemical (10035745)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Soft tissue injury (10041291)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Thermal burn (10053615)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Dehydration (10012174)	5	0.2	0.0	0.4	2	0.1	0.0	0.4	-0.03	-0.25	0.30	0.794
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Hypernatraemia (10020679)	0	0.0	0.0	0.1	2	0.1	0.0	0.4	0.12	0.01	0.44	0.045
	Hypoglycaemic seizure (10048803)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Hypokalaemia (10021015)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Hyponatraemic syndrome (10021037)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Kwashiorkor (10023504)	4	0.1	0.0	0.3	4	0.2	0.1	0.6	0.12	-0.11	0.51	0.313
	Malnutrition (10061273)	5	0.2	0.0	0.4	0	0.0	0.0	0.2	-0.15	-0.35	0.08	0.115
	Marasmus (10026820)	2	0.1	0.0	0.2	1	0.1	0.0	0.3	0.00	-0.17	0.29	0.997
	Metabolic acidosis (10027417)	0	0.0	0.0	0.1	3	0.2	0.0	0.5	0.18	0.06	0.54	0.014
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)	Neuroblastoma (10029260)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Encephalitis (10014581)	1	0.0	0.0	0.2	2	0.1	0.0	0.4	0.09	-0.07	0.41	0.219

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Febrile convulsion (10016284)	6	0.2	0.1	0.4	5	0.3	0.1	0.7	0.12	-0.15	0.54	0.389
	Fontanelle bulging (10016945)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Hydrocephalus (10020508)	0	0.0	0.0	0.1	2	0.1	0.0	0.4	0.12	0.01	0.44	0.045
	Status epilepticus (10041962)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
Renal and urinary disorders (10038359)	Renal failure (10038435)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Aspiration (10003504)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Asthma (10003553)	2	0.1	0.0	0.2	2	0.1	0.0	0.4	0.06	-0.12	0.39	0.476
	Atelectasis (10003598)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Bronchospasm (10006482)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Dyspnoea (10013968)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Epistaxis (10015090)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Grunting (10018762)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Pneumothorax (10035759)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Respiratory arrest (10038669)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Respiratory distress (10038687)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Respiratory failure (10038695)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Skin and subcutaneous tissue disorders (10040785)	Eczema (10014184)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Urticaria (10046735)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Surgical and medical procedures (10042613)	Adenoidectomy (10001230)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Vascular disorders (10047065)	Hypovolaemic shock (10021138)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs, whatever the MedDRA preferred term (PT)

n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 238 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	0	0.0	0.0	0.2	3	0.2	0.0	0.5	3	0.1	0.0	0.3	0	0.0	0.0	0.2
Infections and infestations (10021881)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	3	0.1	0.0	0.3	0	0.0	0.0	0.2

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs assessed as related to vaccination
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 239 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 1 South Africa)

	HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	0	0.0	0.0	0.6	2	0.3	0.0	1.2	2	0.2	0.0	0.6	0	0.0	0.0	0.6
Infections and infestations (10021881)	0	0.0	0.0	0.6	2	0.3	0.0	1.2	2	0.2	0.0	0.6	0	0.0	0.0	0.6

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs assessed as related to vaccination
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 240 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 2 South Africa)

	HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Infections and infestations (10021881)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs assessed as related to vaccination
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 241 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, South Africa)

	HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	0	0.0	0.0	0.3	3	0.3	0.1	0.8	3	0.1	0.0	0.4	0	0.0	0.0	0.4
Infections and infestations (10021881)	0	0.0	0.0	0.3	3	0.3	0.1	0.8	3	0.1	0.0	0.4	0	0.0	0.0	0.4

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs assessed as related to vaccination
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 242 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Malawi)

No records exist in this table.

Supplement 243 Percentage of HIV positive subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

No records exist in this table.

Supplement 244 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

No records exist in this table.

Supplement 245 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	3	0.2	0.0	0.5	0	0.0	0.0	0.2	-0.18	-0.53	0.05	0.084
Infections and infestations (10021881)	3	0.2	0.0	0.5	0	0.0	0.0	0.2	-0.18	-0.53	0.05	0.084

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs assessed as related to vaccination
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 246 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	3	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.09	-0.27	0.14	0.222
Infections and infestations (10021881)	3	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.09	-0.27	0.14	0.222

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified SAEs assessed as related to vaccination
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 247 Percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 1)

		HRV_2D N = 610				HRV_3D N = 612				HRV_POOL N = 1222				Placebo N = 605			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		0	0.0	0.0	0.6	2	0.3	0.0	1.2	2	0.2	0.0	0.6	0	0.0	0.0	0.6
Infections and infestations (10021881)	Sepsis (10040047)	0	0.0	0.0	0.6	2	0.3	0.0	1.2	2	0.2	0.0	0.6	0	0.0	0.0	0.6

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 248 Percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Cohort 2 South Africa)

		HRV_2D N = 447				HRV_3D N = 447				HRV_POOL N = 894				Placebo N = 445			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8
Infections and infestations (10021881)	Otitis media acute (10033079)	0	0.0	0.0	0.8	1	0.2	0.0	1.2	1	0.1	0.0	0.6	0	0.0	0.0	0.8

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 249 Percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, South Africa)

		HRV_2D N = 1057				HRV_3D N = 1059				HRV_POOL N = 2116				Placebo N = 1050			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		0	0.0	0.0	0.3	3	0.3	0.1	0.8	3	0.1	0.0	0.4	0	0.0	0.0	0.4
Infections and infestations (10021881)	Otitis media acute (10033079)	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.0	0.0	0.3	0	0.0	0.0	0.4
	Sepsis (10040047)	0	0.0	0.0	0.3	2	0.2	0.0	0.7	2	0.1	0.0	0.3	0	0.0	0.0	0.4

At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 250 Percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort, Malawi)

No records exist in this table.

Supplement 251 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

No records exist in this table.

Supplement 252 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		3	0.2	0.0	0.5	0	0.0	0.0	0.2	-0.18	-0.53	0.05	0.084
Infections and infestations (10021881)	Otitis media acute (10033079)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Sepsis (10040047)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 253 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with SAEs assessed as related to vaccination classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		3	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.09	-0.27	0.14	0.222
Infections and infestations (10021881)	Otitis media acute (10033079)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Sepsis (10040047)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one SAEs assessed as related to vaccination, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified SAEs
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified SAEs after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 254 Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		42	2.6	1.8	3.4	41	2.5	1.8	3.4	83	2.5	2.0	3.1	43	2.6	1.9	3.5
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Haemorrhagic disorder (10019009)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Gastrointestinal disorders (10017947)	Gastrointestinal disorder (10017944)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Ileus paralytic (10021333)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Intestinal obstruction (10022687)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
General disorders and administration site conditions (10018065)	Death (10011906)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	4	0.1	0.0	0.3	0	0.0	0.0	0.2
	Pyrexia (10037660)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sudden death (10042434)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	2	0.1	0.0	0.4
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3
	Bronchiolitis (10006448)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Bronchopneumonia (10006469)	6	0.4	0.1	0.8	4	0.2	0.1	0.6	10	0.3	0.1	0.6	3	0.2	0.0	0.5
	Gastroenteritis (10017888)	18	1.1	0.6	1.7	11	0.7	0.3	1.2	29	0.9	0.6	1.3	17	1.0	0.6	1.7
	Klebsiella bacteraemia (10058856)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Malaria (10025487)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	4	0.2	0.1	0.6
	Meningitis (10027199)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Meningitis bacterial (10027202)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Meningitis pneumococcal (10027253)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Nosocomial infection (10029803)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Pneumocystis jiroveci pneumonia (10064108)	3	0.2	0.0	0.5	3	0.2	0.0	0.5	6	0.2	0.1	0.4	2	0.1	0.0	0.4
	Pneumonia (10035664)	12	0.7	0.4	1.3	12	0.7	0.4	1.3	24	0.7	0.5	1.1	15	0.9	0.5	1.5

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	Pulmonary tuberculosis (10037440)	2	0.1	0.0	0.4	1	0.1	0.0	0.3	3	0.1	0.0	0.3	1	0.1	0.0	0.3
	Respiratory tract infection (10062352)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Sepsis (10040047)	8	0.5	0.2	1.0	3	0.2	0.0	0.5	11	0.3	0.2	0.6	0	0.0	0.0	0.2
	Septic shock (10040070)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Injury, poisoning and procedural complications (10022117)	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Dehydration (10012174)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	3	0.1	0.0	0.3	1	0.1	0.0	0.3
	Electrolyte imbalance (10014418)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Kwashiorkor (10023504)	3	0.2	0.0	0.5	1	0.1	0.0	0.3	4	0.1	0.0	0.3	0	0.0	0.0	0.2
	Malnutrition (10061273)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Marasmus (10026820)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	2	0.1	0.0	0.2	1	0.1	0.0	0.3
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Nervous system disorders (10029205)	Convulsion (10010904)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Hydrocephalus (10020508)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Status epilepticus	1	0.1	0.0	0.3	1	0.1	0.0	0.3	2	0.1	0.0	0.2	0	0.0	0.0	0.2

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
	(10041962)																
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Aspiration (10003504)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Dyspnoea (10013968)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Grunting (10018762)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2
	Respiratory arrest (10038669)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
	Respiratory distress (10038687)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Respiratory failure (10038695)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Vascular disorders (10047065)	Hypovolaemic shock (10021138)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2

At least one symptom = number of subjects who died during the specified period, whatever the MedDRA preferred term (PT)
n (%)= number (percentage) of subjects reporting the fatal specified symptom
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 255 Percentage of subjects with fatalities due to MedDRA high level term 'Lower respiratory tract and lung infections' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		18	1.1	0.6	1.7	16	1.0	0.6	1.6	34	1.0	0.7	1.4	19	1.2	0.7	1.8
Infections and infestations (10021881)	Bronchopneumonia (10006469)	6	0.4	0.1	0.8	4	0.2	0.1	0.6	10	0.3	0.1	0.6	3	0.2	0.0	0.5
	Lower respiratory tract infection (10024968)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
	Pneumonia (10035664)	12	0.7	0.4	1.3	12	0.7	0.4	1.3	24	0.7	0.5	1.1	15	0.9	0.5	1.5

N = number of subjects with at least one administered dose
At least one symptom = number of subjects who died due to 'Lower respiratory tract and lung infections' during the specified period
n (%)= number (percentage) of subjects reporting the death due to 'Lower respiratory tract and lung infections'
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 256 Percentage of subjects with fatalities due to 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		23	1.4	0.9	2.1	19	1.2	0.7	1.8	42	1.3	0.9	1.7	20	1.2	0.7	1.9
Infections and infestations (10021881)	Bronchopneumonia (10006469)	6	0.4	0.1	0.8	4	0.2	0.1	0.6	10	0.3	0.1	0.6	3	0.2	0.0	0.5
	Pneumocystis jiroveci pneumonia (10064108)	3	0.2	0.0	0.5	3	0.2	0.0	0.5	6	0.2	0.1	0.4	2	0.1	0.0	0.4
	Pneumonia (10035664)	12	0.7	0.4	1.3	12	0.7	0.4	1.3	24	0.7	0.5	1.1	15	0.9	0.5	1.5
Respiratory, thoracic and mediastinal disorders (10038738)	Pneumonia aspiration (10035669)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	0	0.0	0.0	0.2

At least one symptom = number of subjects who died due to 'Pneumonia disease' during the specified period
n (%)= number (percentage) of subjects reporting the death due to 'Pneumonia disease'
N = number of subjects with at least one administered dose
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Supplement 257 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	42	2.6	1.8	3.4	43	2.6	1.9	3.5	0.07	-1.03	1.18	0.899
Blood and lymphatic system disorders (10005329)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.561
Gastrointestinal disorders (10017947)	3	0.2	0.0	0.5	1	0.1	0.0	0.3	-0.12	-0.48	0.18	0.319
General disorders and administration site conditions (10018065)	2	0.1	0.0	0.4	4	0.2	0.1	0.6	0.12	-0.22	0.52	0.411
Immune system disorders (10021428)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	38	2.3	1.6	3.2	35	2.1	1.5	3.0	-0.17	-1.21	0.85	0.734
Injury, poisoning and procedural complications (10022117)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Metabolism and nutrition disorders (10027433)	6	0.4	0.1	0.8	4	0.2	0.1	0.6	-0.12	-0.58	0.30	0.530
Nervous system disorders (10029205)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.997

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 258 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	41	2.5	1.8	3.4	43	2.6	1.9	3.5	0.14	-0.96	1.24	0.803
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Gastrointestinal disorders (10017947)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	4	0.2	0.1	0.6	4	0.2	0.1	0.6	0.00	-0.41	0.41	0.993
Immune system disorders (10021428)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	31	1.9	1.3	2.7	35	2.1	1.5	3.0	0.26	-0.72	1.25	0.601
Injury, poisoning and procedural complications (10022117)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Metabolism and nutrition disorders (10027433)	5	0.3	0.1	0.7	4	0.2	0.1	0.6	-0.06	-0.49	0.36	0.745
Nervous system disorders (10029205)	2	0.1	0.0	0.4	1	0.1	0.0	0.3	-0.06	-0.39	0.23	0.567
Respiratory, thoracic and mediastinal disorders (10038738)	4	0.2	0.1	0.6	2	0.1	0.0	0.4	-0.12	-0.51	0.23	0.418
Vascular disorders (10047065)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 259 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	83	2.5	2.0	3.1	43	2.6	1.9	3.5	0.10	-0.79	1.11	0.828
Blood and lymphatic system disorders (10005329)	1	0.0	0.0	0.2	2	0.1	0.0	0.4	0.09	-0.07	0.41	0.219
Congenital, familial and genetic disorders (10010331)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Gastrointestinal disorders (10017947)	3	0.1	0.0	0.3	1	0.1	0.0	0.3	-0.03	-0.22	0.26	0.727
General disorders and administration site conditions (10018065)	6	0.2	0.1	0.4	4	0.2	0.1	0.6	0.06	-0.20	0.46	0.649
Immune system disorders (10021428)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Infections and infestations (10021881)	69	2.1	1.6	2.6	35	2.1	1.5	3.0	0.04	-0.77	0.97	0.925
Injury, poisoning and procedural complications (10022117)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Metabolism and nutrition disorders (10027433)	11	0.3	0.2	0.6	4	0.2	0.1	0.6	-0.09	-0.40	0.31	0.589
Nervous system disorders (10029205)	3	0.1	0.0	0.3	1	0.1	0.0	0.3	-0.03	-0.22	0.26	0.727
Respiratory, thoracic and mediastinal disorders (10038738)	6	0.2	0.1	0.4	2	0.1	0.0	0.4	-0.06	-0.30	0.27	0.621
Vascular disorders (10047065)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 260 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with fatalities due to 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	23	1.4	0.9	2.1	20	1.2	0.7	1.9	-0.18	-0.99	0.62	0.654
Infections and infestations (10021881)	21	1.3	0.8	1.9	20	1.2	0.7	1.9	-0.06	-0.85	0.73	0.884
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once 'Pneumonia disease' related to death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified 'Pneumonia disease' related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 261 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with fatalities due to 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	19	1.2	0.7	1.8	20	1.2	0.7	1.9	0.07	-0.70	0.84	0.857
Infections and infestations (10021881)	19	1.2	0.7	1.8	20	1.2	0.7	1.9	0.07	-0.70	0.84	0.857

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once 'Pneumonia disease' related to death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified 'Pneumonia disease' related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 262 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with fatalities due to 'Pneumonia disease' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	42	1.3	0.9	1.7	20	1.2	0.7	1.9	-0.05	-0.68	0.68	0.871
Infections and infestations (10021881)	40	1.2	0.9	1.6	20	1.2	0.7	1.9	0.01	-0.61	0.73	0.986
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once 'Pneumonia disease' related to death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified 'Pneumonia disease' related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 263 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with fatalities due to 'Lower respiratory tract and lung infections' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	18	1.1	0.6	1.7	19	1.2	0.7	1.8	0.06	-0.69	0.82	0.860
Infections and infestations (10021881)	18	1.1	0.6	1.7	19	1.2	0.7	1.8	0.06	-0.69	0.82	0.860

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once 'Lower respiratory tract and lung infections' related to death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified 'Lower respiratory tract and lung infections' related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 264 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with fatalities due to 'Lower respiratory tract and lung infections' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	16	1.0	0.6	1.6	19	1.2	0.7	1.8	0.19	-0.54	0.93	0.598
Infections and infestations (10021881)	16	1.0	0.6	1.6	19	1.2	0.7	1.8	0.19	-0.54	0.93	0.598

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once 'Lower respiratory tract and lung infections' related to death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified 'Lower respiratory tract and lung infections' related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 265 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with fatalities due to 'Lower respiratory tract and lung infections' occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	34	1.0	0.7	1.4	19	1.2	0.7	1.8	0.13	-0.46	0.83	0.683
Infections and infestations (10021881)	34	1.0	0.7	1.4	19	1.2	0.7	1.8	0.13	-0.46	0.83	0.683

N = number of subjects with at least one administered dose
n (%)= number (percentage) of subjects reporting at least once 'Lower respiratory tract and lung infections' related to death
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified 'Lower respiratory tract and lung infections' related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 266 Relative risk stratified by dose between pooled HRV group and placebo group for percentages of subjects with fatalities occurring from dose 1 of the HRV vaccine or placebo up to visit 6 (Total vaccinated cohort, HIV negative subjects)

HRV Pool Over Placebo	Value
P-value	0.127
RR	1.998
95%CI LL	0.691
95%CI UL	7.094

RR=relative risk
95%CI=exact 95% confidence interval, LL=lower limit, UL= upper limit
P-value= two sided exact p-value adjusted for those effect for null hypothesis that the relative risk equals one
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 267 Relative risk stratified by dose between pooled HRV group and placebo group for percentages of subjects with fatalities occurring from dose 1 of the HRV vaccine or placebo up to visit 6 (Total vaccinated cohort, HIV positive subjects)

HRV Pool Over Placebo	Value
P-value	0.330
RR	0.595
95%CI LL	0.125
95%CI UL	3.100

RR=relative risk
95%CI=exact 95% confidence interval, LL=lower limit, UL= upper limit
P-value= two sided exact p-value adjusted for those effect for null hypothesis that the relative risk equals one
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 268 Relative risk stratified by dose between pooled HRV group and placebo group for percentages of subjects with fatalities occurring from dose 1 of the HRV vaccine or placebo up to visit 6 (Total vaccinated cohort, HIV unknown subjects)

HRV Pool Over Placebo	Value
P-value	0.160
RR	0.791
95%CI LL	0.511
95%CI UL	1.232

RR=relative risk
95%CI=exact 95% confidence interval, LL=lower limit, UL= upper limit
P-value= two sided exact p-value adjusted for those effect for null hypothesis that the relative risk equals one
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 269 Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				HRV_3D N = 1651				HRV_POOL N = 3298				Placebo N = 1641			
			95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	46	2.8	2.1	3.7	45	2.7	2.0	3.6	91	2.8	2.2	3.4	44	2.7	2.0	3.6
Blood and lymphatic system disorders (10005329)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	2	0.1	0.0	0.2	1	0.1	0.0	0.3
Cardiac disorders (10007541)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Congenital, familial and genetic disorders (10010331)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	0	0.0	0.0	0.2
Gastrointestinal disorders (10017947)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
General disorders and administration site conditions (10018065)	2	0.1	0.0	0.4	4	0.2	0.1	0.6	6	0.2	0.1	0.4	4	0.2	0.1	0.6
Immune system disorders (10021428)	0	0.0	0.0	0.2	0	0.0	0.0	0.2	0	0.0	0.0	0.1	1	0.1	0.0	0.3
Infections and infestations (10021881)	39	2.4	1.7	3.2	33	2.0	1.4	2.8	72	2.2	1.7	2.7	31	1.9	1.3	2.7
Injury, poisoning and procedural complications (10022117)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	1	0.0	0.0	0.2	1	0.1	0.0	0.3
Metabolism and nutrition disorders (10027433)	2	0.1	0.0	0.4	4	0.2	0.1	0.6	6	0.2	0.1	0.4	3	0.2	0.0	0.5
Nervous system disorders (10029205)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	3	0.1	0.0	0.3	2	0.1	0.0	0.4
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	3	0.2	0.0	0.5	5	0.2	0.0	0.4	2	0.1	0.0	0.4

At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)
%= percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
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

Supplement 270 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	46	2.8	2.1	3.7	44	2.7	2.0	3.6	-0.11	-1.25	1.02	0.844
Blood and lymphatic system disorders (10005329)	2	0.1	0.0	0.4	1	0.1	0.0	0.3	-0.06	-0.39	0.23	0.566
Gastrointestinal disorders (10017947)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	2	0.1	0.0	0.4	4	0.2	0.1	0.6	0.12	-0.22	0.52	0.411
Immune system disorders (10021428)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	39	2.4	1.7	3.2	31	1.9	1.3	2.7	-0.48	-1.50	0.52	0.342
Injury, poisoning and procedural complications (10022117)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Metabolism and nutrition disorders (10027433)	2	0.1	0.0	0.4	3	0.2	0.0	0.5	0.06	-0.28	0.43	0.652
Nervous system disorders (10029205)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Respiratory, thoracic and mediastinal disorders (10038738)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.997

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 271 Statistical comparisons between groups (HRV 3 doses and Placebo) for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	45	2.7	2.0	3.6	44	2.7	2.0	3.6	-0.04	-1.17	1.08	0.938
Blood and lymphatic system disorders (10005329)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Cardiac disorders (10007541)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Congenital, familial and genetic disorders (10010331)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Gastrointestinal disorders (10017947)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	4	0.2	0.1	0.6	4	0.2	0.1	0.6	0.00	-0.41	0.41	0.993
Immune system disorders (10021428)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	33	2.0	1.4	2.8	31	1.9	1.3	2.7	-0.11	-1.08	0.86	0.820
Injury, poisoning and procedural complications (10022117)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
Metabolism and nutrition disorders (10027433)	4	0.2	0.1	0.6	3	0.2	0.0	0.5	-0.06	-0.46	0.32	0.711
Nervous system disorders (10029205)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.42	0.28	0.659
Respiratory, thoracic and mediastinal disorders (10038738)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.42	0.28	0.659

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 272 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

	HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
			95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom	91	2.8	2.2	3.4	44	2.7	2.0	3.6	-0.08	-1.00	0.95	0.874
Blood and lymphatic system disorders (10005329)	2	0.1	0.0	0.2	1	0.1	0.0	0.3	0.00	-0.17	0.29	0.997
Cardiac disorders (10007541)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Congenital, familial and genetic disorders (10010331)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Gastrointestinal disorders (10017947)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
General disorders and administration site conditions (10018065)	6	0.2	0.1	0.4	4	0.2	0.1	0.6	0.06	-0.20	0.46	0.649
Immune system disorders (10021428)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Infections and infestations (10021881)	72	2.2	1.7	2.7	31	1.9	1.3	2.7	-0.29	-1.09	0.60	0.496
Injury, poisoning and procedural complications (10022117)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
Metabolism and nutrition disorders (10027433)	6	0.2	0.1	0.4	3	0.2	0.0	0.5	0.00	-0.25	0.37	0.995
Nervous system disorders (10029205)	3	0.1	0.0	0.3	2	0.1	0.0	0.4	0.03	-0.17	0.36	0.748
Respiratory, thoracic and mediastinal disorders (10038738)	5	0.2	0.0	0.4	2	0.1	0.0	0.4	-0.03	-0.25	0.30	0.794

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 273 Statistical comparisons between groups (HRV 2 doses and placebo) for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		46	2.8	2.1	3.7	44	2.7	2.0	3.6	-0.11	-1.25	1.02	0.844
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
	Lymphadenitis (10025188)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Vomiting (10047700)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	Death (10011906)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Pyrexia (10037660)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sudden death (10042434)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sudden infant death syndrome (10042440)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Bronchiolitis (10006448)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Bronchopneumonia (10006469)	7	0.4	0.2	0.9	3	0.2	0.0	0.5	-0.24	-0.71	0.16	0.207
	Gastroenteritis (10017888)	10	0.6	0.3	1.1	11	0.7	0.3	1.2	0.06	-0.52	0.66	0.820
	Herpes simplex (10019948)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Malaria (10025487)	1	0.1	0.0	0.3	2	0.1	0.0	0.4	0.06	-0.23	0.39	0.561
	Meningitis (10027199)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Pneumocystis jiroveci pneumonia (10064108)	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.43	0.28	0.657
	Pneumonia (10035664)	10	0.6	0.3	1.1	13	0.8	0.4	1.4	0.19	-0.42	0.81	0.524
	Respiratory tract infection (10062352)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sepsis (10040047)	5	0.3	0.1	0.7	0	0.0	0.0	0.2	-0.30	-0.71	-0.07	0.026

		HRV_2D N = 1647				Placebo N = 1641				Difference between Placebo - HRV_2D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
Injury, poisoning and procedural complications (10022117)	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Dehydration (10012174)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.998
	Malnutrition (10061273)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.318
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Nervous system disorders (10029205)	Hydrocephalus (10020508)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
Respiratory, thoracic and mediastinal disorders (10038738)	Dyspnoea (10013968)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Grunting (10018762)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Respiratory distress (10038687)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA prefered term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups
by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 274 Statistical comparisons between groups (HRV 3 doses and placebo) for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		45	2.7	2.0	3.6	44	2.7	2.0	3.6	-0.04	-1.17	1.08	0.938
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Vomiting (10047700)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
General disorders and administration site conditions (10018065)	Death (10011906)	2	0.1	0.0	0.4	0	0.0	0.0	0.2	-0.12	-0.44	0.11	0.158
	Pyrexia (10037660)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sudden death (10042434)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sudden infant death syndrome (10042440)	2	0.1	0.0	0.4	2	0.1	0.0	0.4	0.00	-0.33	0.33	0.995
Immune system disorders (10021428)	Immunosuppressio n (10062016)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	1	0.1	0.0	0.3	1	0.1	0.0	0.3	0.00	-0.29	0.29	0.997
	Bronchopneumonia (10006469)	0	0.0	0.0	0.2	3	0.2	0.0	0.5	0.18	-0.05	0.54	0.082
	Gastroenteritis (10017888)	9	0.5	0.2	1.0	11	0.7	0.3	1.2	0.13	-0.44	0.71	0.644
	Malaria (10025487)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Meningitis (10027199)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Meningitis bacterial (10027202)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Meningitis pneumococcal (10027253)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Otitis media acute (10033079)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Pneumocystis	3	0.2	0.0	0.5	2	0.1	0.0	0.4	-0.06	-0.42	0.28	0.659

		HRV_3D N = 1651				Placebo N = 1641				Difference between Placebo - HRV_3D			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	jiroveci pneumonia (10064108)												
	Pneumonia (10035664)	12	0.7	0.4	1.3	13	0.8	0.4	1.4	0.07	-0.57	0.71	0.829
	Pulmonary tuberculosis (10037440)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Respiratory tract infection (10062352)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Sepsis (10040047)	4	0.2	0.1	0.6	0	0.0	0.0	0.2	-0.24	-0.62	-0.01	0.046
Injury, poisoning and procedural complications (10022117)	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Vaccination complication (10046861)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Dehydration (10012174)	2	0.1	0.0	0.4	1	0.1	0.0	0.3	-0.06	-0.39	0.23	0.567
	Kwashiorkor (10023504)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Marasmus (10026820)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Metabolic acidosis (10027417)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Febrile convulsion (10016284)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Hydrocephalus (10020508)	0	0.0	0.0	0.2	2	0.1	0.0	0.4	0.12	-0.11	0.44	0.156
	Status epilepticus (10041962)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Aspiration (10003504)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Dyspnoea (10013968)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Grunting (10018762)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316
	Respiratory arrest (10038669)	1	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.06	-0.34	0.17	0.319
	Respiratory distress (10038687)	0	0.0	0.0	0.2	1	0.1	0.0	0.3	0.06	-0.17	0.34	0.316

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA prefered term (PT)

n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups
by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 275 Statistical comparisons between groups (HRV pool and placebo) for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
At least one symptom		91	2.8	2.2	3.4	44	2.7	2.0	3.6	-0.08	-1.00	0.95	0.874
Blood and lymphatic system disorders (10005329)	Anaemia (10002034)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Lymphadenitis (10025188)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Cardiac disorders (10007541)	Cardiac failure congestive (10007559)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Congenital, familial and genetic disorders (10010331)	Heart disease congenital (10019273)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Vomiting (10047700)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
General disorders and administration site conditions (10018065)	Death (10011906)	4	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.12	-0.31	0.11	0.158
	Pyrexia (10037660)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Sudden death (10042434)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Sudden infant death syndrome (10042440)	2	0.1	0.0	0.2	2	0.1	0.0	0.4	0.06	-0.12	0.39	0.476
Immune system disorders (10021428)	Immunosuppression (10062016)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
Infections and infestations (10021881)	Acquired immunodeficiency syndrome (10000565)	1	0.0	0.0	0.2	1	0.1	0.0	0.3	0.03	-0.12	0.32	0.614
	Bronchiolitis (10006448)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	Bronchopneumonia (10006469)	7	0.2	0.1	0.4	3	0.2	0.0	0.5	-0.03	-0.29	0.34	0.828
	Gastroenteritis (10017888)	19	0.6	0.3	0.9	11	0.7	0.3	1.2	0.09	-0.34	0.66	0.688
	Herpes simplex (10019948)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Malaria (10025487)	1	0.0	0.0	0.2	2	0.1	0.0	0.4	0.09	-0.07	0.41	0.219
	Meningitis (10027199)	3	0.1	0.0	0.3	0	0.0	0.0	0.2	-0.09	-0.27	0.14	0.222
	Meningitis bacterial (10027202)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Meningitis pneumococcal (10027253)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Otitis media acute (10033079)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Pneumocystis jiroveci pneumonia (10064108)	6	0.2	0.1	0.4	2	0.1	0.0	0.4	-0.06	-0.30	0.27	0.621
	Pneumonia (10035664)	22	0.7	0.4	1.0	13	0.8	0.4	1.4	0.13	-0.35	0.73	0.621
	Pulmonary tuberculosis (10037440)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Respiratory tract infection (10062352)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Sepsis (10040047)	9	0.3	0.1	0.5	0	0.0	0.0	0.2	-0.27	-0.52	-0.04	0.034
Injury, poisoning and procedural complications (10022117)	Therapeutic agent toxicity (10043408)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Vaccination complication (10046861)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Metabolism and nutrition disorders (10027433)	Cachexia (10006895)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Dehydration (10012174)	3	0.1	0.0	0.3	1	0.1	0.0	0.3	-0.03	-0.22	0.26	0.727
	Kwashiorkor (10023504)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Malnutrition (10061273)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Marasmus (10026820)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Metabolic acidosis	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156

		HRV_POOL N = 3298				Placebo N = 1641				Difference between Placebo - HRV_POOL			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	%	LL	UL	P-Value
	(10027417)												
Nervous system disorders (10029205)	Convulsion (10010904)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Febrile convulsion (10016284)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Hydrocephalus (10020508)	0	0.0	0.0	0.1	2	0.1	0.0	0.4	0.12	0.01	0.44	0.045
	Status epilepticus (10041962)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
Respiratory, thoracic and mediastinal disorders (10038738)	Asphyxia (10003497)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Aspiration (10003504)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Dyspnoea (10013968)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Grunting (10018762)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156
	Pneumonia aspiration (10035669)	2	0.1	0.0	0.2	0	0.0	0.0	0.2	-0.06	-0.22	0.17	0.318
	Respiratory arrest (10038669)	1	0.0	0.0	0.2	0	0.0	0.0	0.2	-0.03	-0.17	0.20	0.481
	Respiratory distress (10038687)	0	0.0	0.0	0.1	1	0.1	0.0	0.3	0.06	-0.06	0.34	0.156

N = number of subjects with at least one administered dose
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA prefered term (PT)
n (%)= number (percentage) of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI* = 95% confidence interval for difference in proportions (Standardized asymptotic)
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-Value = 2-sided P-value (Standardized asymptotic)
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups
by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)

Supplement 276 Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

[redacted]

Supplement 277 Summary of HIV concomitant medication during the study (Total vaccinated cohort)

		HRV_2D N = 1647		HRV_3D N = 1651		HRV_POOL N = 3298		Placebo N = 1641		Total N = 4939	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Therapeutic HIV medication	Yes	0	0.0	1	0.1	1	0.0	4	0.2	5	0.1
	No	1647	100	1650	99.9	3297	100	1637	99.8	4934	99.9
HIV medication	Yes	67	4.1	64	3.9	131	4.0	76	4.6	207	4.2
	No	1580	95.9	1587	96.1	3167	96.0	1565	95.4	4732	95.8

HRV_2D = GR3**HRV 2 doses
HRV_3D = GR2**HRV 3 doses
HRV_POOL = GR2**HRV 3 doses/GR3**HRV 2 doses
Placebo = GR1**Placebo
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 278 Summary of HIV concomitant medication during the study (Total vaccinated cohort, Cohort 1 South Africa)

		HRV_2D N = 610		HRV_3D N = 612		HRV_POOL N = 1222		Placebo N = 605		Total N = 1827	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Therapeutic HIV medication	Yes	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
	No	610	100	612	100	1222	100	604	99.8	1826	99.9
HIV medication	Yes	4	0.7	4	0.7	8	0.7	3	0.5	11	0.6
	No	606	99.3	608	99.3	1214	99.3	602	99.5	1816	99.4

HRV_2D = GR3**HRV 2 doses
HRV_3D = GR2**HRV 3 doses
HRV_POOL = GR2**HRV 3 doses/GR3**HRV 2 doses
Placebo = GR1**Placebo
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 279 Summary of HIV concomitant medication during the study (Total vaccinated cohort, Cohort 2 South Africa)

		HRV_2D N = 447		HRV_3D N = 447		HRV_POOL N = 894		Placebo N = 445		Total N = 1339	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Therapeutic HIV medication	Yes	0	0.0	1	0.2	1	0.1	2	0.4	3	0.2
	No	447	100	446	99.8	893	99.9	443	99.6	1336	99.8
HIV medication	Yes	48	10.7	39	8.7	87	9.7	54	12.1	141	10.5
	No	399	89.3	408	91.3	807	90.3	391	87.9	1198	89.5

HRV_2D = GR3**HRV 2 doses
HRV_3D = GR2**HRV 3 doses
HRV_POOL = GR2**HRV 3 doses/GR3**HRV 2 doses
Placebo = GR1**Placebo
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 280 Summary of HIV concomitant medication during the study (Total vaccinated cohort, South Africa)

		HRV_2D N = 1057		HRV_3D N = 1059		HRV_POOL N = 2116		Placebo N = 1050		Total N = 3166	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Therapeutic HIV medication	Yes	0	0.0	1	0.1	1	0.0	3	0.3	4	0.1
	No	1057	100	1058	99.9	2115	100	1047	99.7	3162	99.9
HIV medication	Yes	52	4.9	43	4.1	95	4.5	57	5.4	152	4.8
	No	1005	95.1	1016	95.9	2021	95.5	993	94.6	3014	95.2

HRV_2D = GR3**HRV 2 doses
HRV_3D = GR2**HRV 3 doses
HRV_POOL = GR2**HRV 3 doses/GR3**HRV 2 doses
Placebo = GR1**Placebo
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 281 Summary of HIV concomitant medication during the study (Total vaccinated cohort, Malawi)

		HRV_2D N = 590		HRV_3D N = 592		HRV_POOL N = 1182		Placebo N = 591		Total N = 1773	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Therapeutic HIV medication	Yes	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
	No	590	100	592	100	1182	100	590	99.8	1772	99.9
HIV medication	Yes	15	2.5	21	3.5	36	3.0	19	3.2	55	3.1
	No	575	97.5	571	96.5	1146	97.0	572	96.8	1718	96.9

HRV_2D = GR3**HRV 2 doses
HRV_3D = GR2**HRV 3 doses
HRV_POOL = GR2**HRV 3 doses/GR3**HRV 2 doses
Placebo = GR1**Placebo
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

Supplement 282 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity, South Africa cohort 1)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	70	0	0.0	0.0	5.1	<20	-	-
	PIII(M3)	447	286	64.0	59.3	68.4	63.4	53.8	74.6
HRV_3D	PRE	66	0	0.0	0.0	5.4	<20	-	-
	PIII(M3)	424	256	60.4	55.5	65.1	58.6	49.3	69.5
HRV_POOL	PRE	136	0	0.0	0.0	2.7	<20	-	-
	PIII(M3)	871	542	62.2	58.9	65.5	61.0	54.2	68.6
Placebo	PRE	69	0	0.0	0.0	5.2	<20	-	-
	PIII(M3)	434	52	12.0	9.1	15.4	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 283 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity, South Africa cohort 2)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PIII(M3)	382	269	70.4	65.6	75.0	84.6	70.2	102.0
HRV_3D	PIII(M3)	393	260	66.2	61.2	70.8	77.9	64.4	94.2
HRV_POOL	PIII(M3)	775	529	68.3	64.9	71.5	81.1	71.0	92.7
Placebo	PIII(M3)	379	84	22.2	18.1	26.7	21.2	18.0	24.9

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results; n (%) = number (percentage) of subjects with concentration above the cut-off; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 284 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity, South Africa)

			≥20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	70	0	0.0	0.0	5.1	<20	-	-
	PIII(M3)	829	555	66.9	63.6	70.1	72.4	64.0	81.9
HRV_3D	PRE	66	0	0.0	0.0	5.4	<20	-	-
	PIII(M3)	817	516	63.2	59.7	66.5	67.2	59.1	76.3
HRV_POOL	PRE	136	0	0.0	0.0	2.7	<20	-	-
	PIII(M3)	1646	1071	65.1	62.7	67.4	69.8	63.8	76.2
Placebo	PRE	69	0	0.0	0.0	5.2	<20	-	-
	PIII(M3)	813	136	16.7	14.2	19.5	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 285 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity, Malawi)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	36	0	0.0	0.0	9.7	<20	-	-
	PIII(M3)	331	201	60.7	55.2	66.0	72.8	59.1	89.7
HRV_3D	PRE	49	0	0.0	0.0	7.3	<20	-	-
	PIII(M3)	321	190	59.2	53.6	64.6	69.8	55.9	87.1
HRV_POOL	PRE	85	0	0.0	0.0	4.2	<20	-	-
	PIII(M3)	652	391	60.0	56.1	63.8	71.3	61.3	83.0
Placebo	PRE	42	0	0.0	0.0	8.4	<20	-	-
	PIII(M3)	312	126	40.4	34.9	46.1	37.0	30.0	45.7

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 286 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity, South Africa cohort 1)

			≥20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	70	0	0.0	0.0	5.1	<20	-	-
	PIII(M3)	70	40	57.1	44.7	68.9	59.4	37.5	93.9
HRV_3D	PRE	66	0	0.0	0.0	5.4	<20	-	-
	PIII(M3)	66	44	66.7	54.0	77.8	94.3	56.5	157.4
HRV_POOL	PRE	136	0	0.0	0.0	2.7	<20	-	-
	PIII(M3)	136	84	61.8	53.0	70.0	74.3	52.9	104.5
Placebo	PRE	69	0	0.0	0.0	5.2	<20	-	-
	PIII(M3)	69	8	11.6	5.1	21.6	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post time points
n (%) = number (percentage) of subjects who seroconverted
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = blood sample taken one months after Dose 3 of HRV vaccine/placebo (visit 4)
PRE = pre-vaccination

Supplement 287 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity, South Africa cohort 2)

No records exist in this table.

Supplement 288 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity, South Africa)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	70	0	0.0	0.0	5.1	<20	-	-
	PIII(M3)	70	40	57.1	44.7	68.9	59.4	37.5	93.9
HRV_3D	PRE	66	0	0.0	0.0	5.4	<20	-	-
	PIII(M3)	66	44	66.7	54.0	77.8	94.3	56.5	157.4
HRV_POOL	PRE	136	0	0.0	0.0	2.7	<20	-	-
	PIII(M3)	136	84	61.8	53.0	70.0	74.3	52.9	104.5
Placebo	PRE	69	0	0.0	0.0	5.2	<20	-	-
	PIII(M3)	69	8	11.6	5.1	21.6	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post time points
n (%) = number (percentage) of subjects who seroconverted
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = blood sample taken one months after Dose 3 of HRV vaccine/placebo (visit 4)
PRE = pre-vaccination

Supplement 289 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity, Malawi)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	36	0	0.0	0.0	9.7	<20	-	-
	PIII(M3)	36	17	47.2	30.4	64.5	51.5	26.0	102.0
HRV_3D	PRE	49	0	0.0	0.0	7.3	<20	-	-
	PIII(M3)	49	28	57.1	42.2	71.2	63.0	36.3	109.2
HRV_POOL	PRE	85	0	0.0	0.0	4.2	<20	-	-
	PIII(M3)	85	45	52.9	41.8	63.9	57.8	37.9	88.1
Placebo	PRE	42	0	0.0	0.0	8.4	<20	-	-
	PIII(M3)	42	17	40.5	25.6	56.7	38.2	21.2	68.5

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post time points
n (%) = number (percentage) of subjects who seroconverted
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = blood sample taken two months after Dose 3 of HRV vaccine/placebo (visit 4)
PRE = pre-vaccination

Supplement 290 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, South Africa cohort 1)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	286	179.1	153.1	209.6
HRV_3D	PIII(M3)	256	186.8	157.4	221.6
HRV_POOL	PIII(M3)	542	182.7	162.8	205.1
Placebo	PIII(M3)	52	353.4	213.7	584.3

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 291 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, South Africa cohort 2)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	269	207.4	173.7	247.6
HRV_3D	PIII(M3)	260	222.7	185.2	267.9
HRV_POOL	PIII(M3)	529	214.8	189.1	244.0
Placebo	PIII(M3)	84	295.1	206.9	420.9

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 292 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, South Africa)

			GMC		
					95% CI
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	555	192.3	171.0	216.3
HRV_3D	PIII(M3)	516	204.1	180.0	231.5
HRV_POOL	PIII(M3)	1071	197.9	181.6	215.6
Placebo	PIII(M3)	136	316.2	237.0	421.7

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 293 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, Malawi)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	201	263.1	217.0	319.0
HRV_3D	PIII(M3)	190	266.4	212.4	334.1
HRV_POOL	PIII(M3)	391	264.7	228.4	306.7
Placebo	PIII(M3)	126	255.8	192.6	339.8

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 294 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, South Africa cohort 1)

			GMC		
					95% CI
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	40	225.8	139.4	365.6
HRV_3D	PIII(M3)	44	289.6	175.7	477.2
HRV_POOL	PIII(M3)	84	257.2	182.7	362.0
Placebo	PIII(M3)	8	1149.6	284.5	4645.6

GMC = geometric mean antibody concentration calculated on subjects with concentration >= 20 U/ML
N = number of subjects who were seronegative for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 295 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, South Africa cohort 2)

No records exist in this table.

Supplement 296 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, South Africa)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	40	225.8	139.4	365.6
HRV_3D	PIII(M3)	44	289.6	175.7	477.2
HRV_POOL	PIII(M3)	84	257.2	182.7	362.0
Placebo	PIII(M3)	8	1149.6	284.5	4645.6

GMC = geometric mean antibody concentration calculated on subjects with concentration >= 20 U/ML
N = number of subjects who were seronegative for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 297 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, Malawi)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	17	321.5	150.2	687.8
HRV_3D	PIII(M3)	28	250.3	146.1	428.7
HRV_POOL	PIII(M3)	45	275.1	180.0	420.4
Placebo	PIII(M3)	17	273.3	129.2	578.3

GMC = geometric mean antibody concentration calculated on subjects with concentration >= 20 U/ML
N = number of subjects who were seronegative for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 298 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity, HIV Positive population)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	1	0	0.0	0.0	97.5	<20	-	-
	PIII(M3)	15	6	40.0	16.3	67.7	28.4	11.8	68.1
HRV_3D	PRE	3	0	0.0	0.0	70.8	<20	-	-
	PIII(M3)	22	16	72.7	49.8	89.3	89.7	34.9	230.8
HRV_POOL	PRE	4	0	0.0	0.0	60.2	<20	-	-
	PIII(M3)	37	22	59.5	42.1	75.2	56.2	29.0	109.1
Placebo	PRE	1	0	0.0	0.0	97.5	<20	-	-
	PIII(M3)	16	3	18.8	4.0	45.6	<20	-	-

GMC = geometric mean antibody concentration calculated on HIV positive subjects
N = number of HIV positive subjects with available results
n (%) = number (percentage) of HIV positive subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 299 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity, HIV positive subjects)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	1	0	0.0	0.0	97.5	<20	-	-
	PIII(M3)	1	0	0.0	0.0	97.5	<20	-	-
HRV_3D	PRE	3	0	0.0	0.0	70.8	<20	-	-
	PIII(M3)	3	1	33.3	0.8	90.6	23.2	0.6	868.6
HRV_POOL	PRE	4	0	0.0	0.0	60.2	<20	-	-
	PIII(M3)	4	1	25.0	0.6	80.6	<20	-	-
Placebo	PRE	1	0	0.0	0.0	97.5	<20	-	-
	PIII(M3)	1	0	0.0	0.0	97.5	<20	-	-

GMC = geometric mean antibody concentration calculated on HIV positive subjects
N = number of subjects with available results at pre and post time points
n (%) = number (percentage) of subjects who seroconverted; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PIII (M3) = blood sample taken two months after Dose 3 of HRV vaccine/placebo (visit 4)
PRE = pre-vaccination

Supplement 300 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, HIV Positive population)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	6	135.5	29.3	625.4
HRV_3D	PIII(M3)	16	204.2	73.1	570.3
HRV_POOL	PIII(M3)	22	182.6	82.6	403.3
Placebo	PIII(M3)	3	252.9	0.8	81143.0

GMC = geometric mean antibody concentration calculated on HIV positive and seropositive subjects
N = number of HIV positive subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 301 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity, HIV positive subjects)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_3D	PIII(M3)	1	125.0	-	-
HRV_POOL	PIII(M3)	1	125.0	-	-

GMC = geometric mean antibody concentration calculated on HIV positive subjects with concentration >= 20 U/ML
N = number of subjects who were seronegative for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 302 Anti-rotavirus IgA antibody GMC and seropositivity rates (Total vaccinated cohort)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	143	17	11.9	7.1	18.4	<20	-	-
	PIII(M3)	1427	914	64.1	61.5	66.5	70.6	64.1	77.8
HRV_3D	PRE	168	15	8.9	5.1	14.3	<20	-	-
	PIII(M3)	1384	863	62.4	59.7	64.9	70.0	63.3	77.5
HRV_POOL	PRE	311	32	10.3	7.1	14.2	<20	-	-
	PIII(M3)	2811	1777	63.2	61.4	65.0	70.3	65.6	75.4
Placebo	PRE	157	18	11.5	6.9	17.5	<20	-	-
	PIII(M3)	1380	348	25.2	22.9	27.6	23.5	21.5	25.7

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 303 Seropositivity rates and GMCs for Rota IgA antibodies (Total vaccinated cohort, South Africa)

				≥ 20 U/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ROTA IgA	HRV_2D	PRE	91	7	7.7	3.1	15.2	<20	-	-
		PIII(M3)	922	612	66.4	63.2	69.4	71.1	63.2	80.0
	HRV_3D	PRE	94	8	8.5	3.7	16.1	<20	-	-
		PIII(M3)	910	571	62.7	59.5	65.9	66.4	58.9	75.0
	HRV_POOL	PRE	185	15	8.1	4.6	13.0	<20	-	-
		PIII(M3)	1832	1183	64.6	62.3	66.8	68.8	63.2	74.8
	Placebo	PRE	90	11	12.2	6.3	20.8	<20	-	-
		PIII(M3)	917	172	18.8	16.3	21.4	<20	-	-

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 304 Seropositivity rates and GMCs for Rota IgA antibodies (Total vaccinated cohort, Malawi)

				≥20 U/ML				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
ROTA IgA	HRV_2D	PRE	52	10	19.2	9.6	32.5	<20	-	-
		PIII(M3)	505	302	59.8	55.4	64.1	69.7	58.8	82.6
	HRV_3D	PRE	74	7	9.5	3.9	18.5	<20	-	-
		PIII(M3)	474	292	61.6	57.1	66.0	77.5	64.5	93.2
	HRV_POOL	PRE	126	17	13.5	8.1	20.7	<20	-	-
		PIII(M3)	979	594	60.7	57.5	63.7	73.4	64.8	83.1
	Placebo	PRE	67	7	10.4	4.3	20.3	<20	-	-
		PIII(M3)	463	176	38.0	33.6	42.6	35.4	29.8	42.0

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 305 Anti-rotavirus IgA antibody GMC and seroconversion rates (Total vaccinated cohort)

			≥ 20 U/ML				GMC		
					95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	value	LL	UL
HRV_2D	PRE	126	0	0.0	0.0	2.9	<20	-	-
	PIII(M3)	111	59	53.2	43.4	62.7	54.7	38.0	78.7
HRV_3D	PRE	153	0	0.0	0.0	2.4	<20	-	-
	PIII(M3)	127	80	63.0	54.0	71.4	81.1	56.9	115.8
HRV_POOL	PRE	279	0	0.0	0.0	1.3	<20	-	-
	PIII(M3)	238	139	58.4	51.9	64.7	67.5	52.4	87.0
Placebo	PRE	139	0	0.0	0.0	2.6	<20	-	-
	PIII(M3)	118	26	22.0	14.9	30.6	23.2	16.8	31.9

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post time points
n (%) = number (percentage) of subjects who seroconverted
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = blood sample taken two months after Dose 3 of HRV vaccine/placebo (visit 4)
PRE = pre-vaccination

Supplement 306 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (Total vaccinated cohort)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PRE	17	103.8	55.8	193.0
	PIII(M3)	914	211.5	192.7	232.3
HRV_3D	PRE	15	105.1	45.9	240.8
	PIII(M3)	863	226.8	205.2	250.7
HRV_POOL	PRE	32	104.4	64.7	168.5
	PIII(M3)	1777	218.8	204.4	234.3
Placebo	PRE	18	122.0	70.1	212.1
	PIII(M3)	348	294.4	247.3	350.5

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)
PRE = pre-vaccination

Supplement 307 GMCs on seropositive subjects for Rota IgA antibodies (Total vaccinated cohort, South Africa)

				GMC		
					95% CI	
Antibody	Group	Timing	N	value	LL	UL
ROTA IgA	HRV_2D	PRE	91	182.0	48.0	689.8
		PIII(M3)	922	192.1	171.5	215.3
	HRV_3D	PRE	94	108.9	30.3	391.5
		PIII(M3)	910	204.4	181.4	230.3
	HRV_POOL	PRE	185	138.4	61.7	310.6
		PIII(M3)	1832	198.0	182.4	214.9
	Placebo	PRE	90	132.5	54.0	325.2
		PIII(M3)	917	312.6	241.3	405.0

GMC = geometric mean antibody concentration calculated on subjects with concentration $\geq$ 20 U/ML
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 308 GMCs on seropositive subjects for Rota IgA antibodies (Total vaccinated cohort, Malawi)

				GMC		
					95% CI	
Antibody	Group	Timing	N	value	LL	UL
ROTA IgA	HRV_2D	PRE	52	70.1	37.2	132.1
		PIII(M3)	505	257.0	218.3	302.7
	HRV_3D	PRE	74	100.9	23.4	434.9
		PIII(M3)	474	278.0	232.0	333.1
	HRV_POOL	PRE	126	81.4	44.2	150.0
		PIII(M3)	979	267.1	236.6	301.6
	Placebo	PRE	67	107.1	55.8	205.7
		PIII(M3)	463	277.7	219.3	351.6

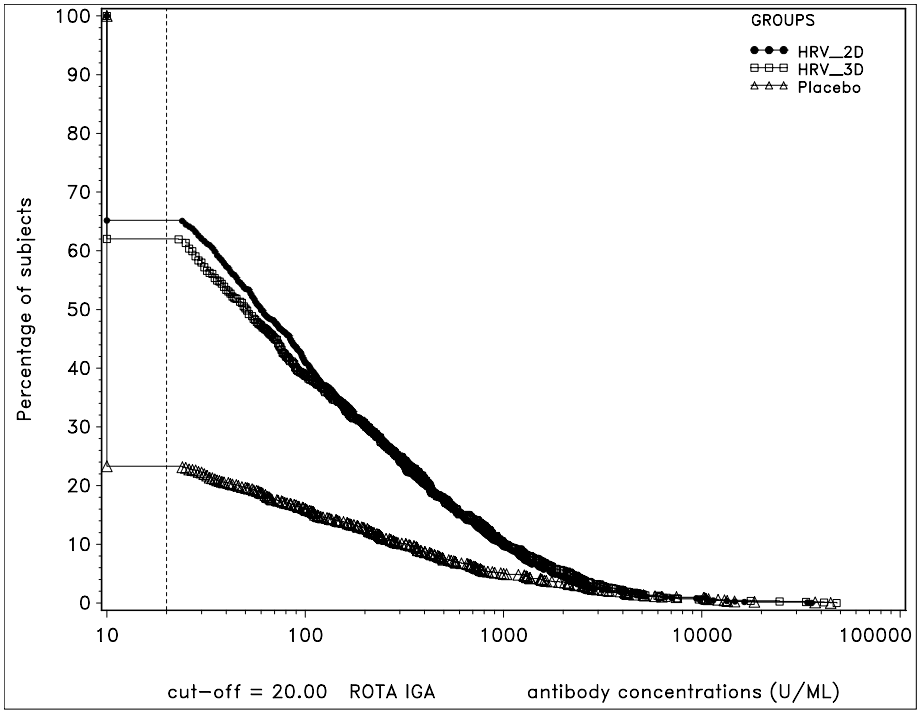
GMC = geometric mean antibody concentration calculated on subjects with concentration >= 20 U/ML
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

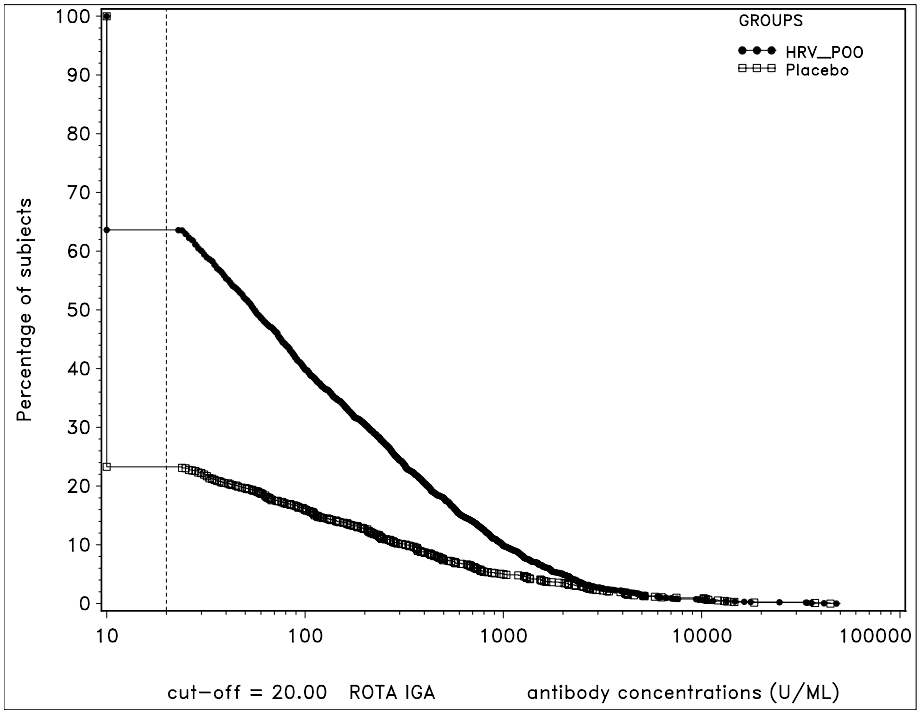
Supplement 309 Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (Total vaccinated cohort)

			GMC		
				95% CI	
Group	Timing	N	value	LL	UL
HRV_2D	PIII(M3)	59	244.7	166.1	360.5
HRV_3D	PIII(M3)	80	277.5	196.6	391.8
HRV_POOL	PIII(M3)	139	263.1	203.9	339.4
Placebo	PIII(M3)	26	451.9	234.5	871.0

GMC = geometric mean antibody concentration calculated on subjects with concentration ≥ 20 U/ML
N = number of subjects who were seronegative for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PIII (M3) = one month after Dose 3 of HRV/placebo vaccine (visit 4)

Supplement 310 Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at visit 4 (Total vaccinated cohort)





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13. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Statistician: [redacted]

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Central Safety Contact: [redacted]

Regulatory Affairs representative: [redacted]

Clinical Development Manager: [redacted]
Director, Rotavirus vaccines
Global Clinical Research and Development

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	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

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-track #
Rota-037	102248

Date: 21 August 2008

***Concerns:* Sponsor Information Sheet**

Details:

This File Note serves to document that the Sponsor Information Sheet for the Rota-037 study is not available for the publishing of the Rota-037 Clinical Study Report. This file notes provides an official record of this process.

GSM Responsible: [redacted]

Signat [redacted]

Signature Date: 21 AUG 2008

Protocol and Protocol Amendments

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GlaxoSmithKline Biologicals
Rue de l'Institut 89
B-1330 Rixensart Belgium

Study vaccine	GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine.
eTrack study number *and abbreviated title*	102248 (Rota-037) ***111274 (ROTA-037 EXT:Y2)*** **(Administrative Change 2: 30 August 2007)**
Date of *protocol*	27 April 2005 – Final Protocol
(Administrative Change 2: 30 August 2007)	24 August 2005 – Amendment 1 22 September 2005 – Administrative change 1 27 October 2005 – Amendment 2 22 February 2006 – Malawi-specific Amendment 3 15 May 2006 – Malawi-specific Amendment 4 10 July 2006 – South Africa-specific Amendment 5 2 August 2007 – Amendment 6 **30 August 2007 – Administrative change 2**
Title	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Co-ordinating authors	[redacted] Scientific Writers (Amendment 6: 2 August 2007)
Contributing authors	[redacted] Director (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007) [redacted] Biostatistician [redacted] Clinical Development Manager [redacted] Central Study Coordinator (Amendment 6: 2 August 2007)

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[redacted] Clinical Development Manager
(Amendment 2: 27 October 2005) (Amendment 6: 2 August 2007)

GSK Biologicals' Protocol V 12.2

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102248 (Rota-037) & 111274 (ROTA-037 EXT:Y2)
Administrative Change 2

Protocol Administrative Change Sponsor Signatory Approval

(Administrative Change 2: 30 August 2007)

eTrack study number *and abbreviated title*	102248 (Rota-037) ***111274 (ROTA-037 EXT:Y2)*** **(Administrative Change 2: 30 August 2007)**
Date of *protocol*	27 April 2005 – Final Protocol
(Administrative Change 2: 30 August 2007)	24 August 2005 – Amendment 1
	22 September 2005 – Administrative change 1
	27 October 2005 – Amendment 2
	22 February 2006 – Malawi-specific Amendment 3
	15 May 2006 – Malawi-specific Amendment 4
	10 July 2006 – South Africa-specific Amendment 5
	2 August 2007 – Amendment 6
	30 August 2007 – Administrative change 2
Title	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Sponsor signatory:	[redacted] Director (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

Signature:

Date:

(Administrative Change 2: 30 August 2007)

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Protocol Administrative Change Investigator Agreement

(Administrative Change 2: 30 August 2007)

eTrack study number *and abbreviated title*	102248 (Rota-037) ***111274 (ROTA-037 EXT:Y2)* (Administrative Change 2: 30 August 2007)**
Date of *protocol*	27 April 2005 – Final Protocol
(Administrative Change 2: 30 August 2007)	24 August 2005 – Amendment 1 22 September 2005 – Administrative change 1 27 October 2005 – Amendment 2 22 February 2006 – Malawi-specific Amendment 3 15 May 2006 – Malawi-specific Amendment 4 10 July 2006 – South Africa-specific Amendment 5 2 August 2007 – Amendment 6 **30 August 2007 – Administrative change 2**
Title	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments, and with any other study conduct procedures provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational products and other study-related duties and functions as described in the protocol.
- Not to implement any changes to the protocol without agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an

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102248 (Rota-037) & 111274 (ROTA-037 EXT:Y2)
Administrative Change 2

immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, for administrative aspects of the study).

- That I am thoroughly familiar with the appropriate use of the vaccine(s), as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), and prescribing information (in the case of a marketed vaccine). (Amendment 2: 27 October 2005)
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals investigational product(s) and other study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name:

Investigator signature ***Date***

(Administrative Change 2: 30 August 2007)

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Synopsis

Title A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)

Indication/Study population Three-dose oral immunisation against human rotavirus disease administered 4 weeks apart.

Healthy infants who are 5-10 weeks of age at the time of the first dose.

Background Rotavirus (RV) is the most important cause of severe gastroenteritis (GE) requiring hospitalisation of infants and young children in developed countries, and is a frequent cause of death in children less than 5 years of age in developing regions of the world. In South Africa, rotavirus is a large health burden in young children accounting for approximately 25% of the diarrhoeal deaths reported. Rotavirus is responsible for approximately 25% of all hospitalisations due to diarrhoeal diseases in young children under five years in South Africa [Cunliffe , 1998; Steele , 2003]. The disease was shown to be seasonal with a clear peak in autumn winter season [Steele , 2003]. It was estimated that an effective vaccine against RV could prevent 16% of all diarrhoeal deaths in children below 5 years of age [De Zoysa, 1985]. To meet the global public health need, GlaxoSmithKline (GSK) Biologicals has developed a monovalent vaccine based on a human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8]. This vaccine has been tested extensively in Phase I, II and III trials and found to be well-tolerated, immunogenic and efficacious in preventing RV GE in infants. A large phase III trial in 63,225 infants demonstrated that the HRV vaccine is not associated with intussusception (IS).

Two phase II trials have been conducted in South Africa. In the first phase II trial in South Africa (study rota-014), two doses of HRV vaccine ($10^{5.2}$ ffu) were administered at 6 and 10 weeks (first study part) or 10 and 14 weeks of age (second study part) concomitantly with oral polio vaccine (OPV) or inactivated polio vaccine (IPV). The objective of this study was to see if HRV vaccine would interfere with the take of OPV. The results of this study demonstrated that immune response to the OPV vaccine did not seem to be affected by co-administration with HRV vaccine. There was an interference of OPV on HRV immunogenicity after the first dose and the interference was overcome by the second dose. There was no interference of co-administered OPV on immunogenicity of HRV vaccine after two doses. Anti-rotavirus IgA antibody seroconversion rate was higher

and the interference of OPV at the first dose was less marked when two doses were given at 10 and 14 weeks of age compared to two doses given at 6 and 10 weeks of age. In the next phase II study (study rota-013) in South Africa, two doses of HRV vaccine ($10^{6.5}$ $CCID_{50}$) administered at 10 and 14 weeks were compared with three doses administered at 6, 10 and 14 weeks of age when given concomitantly with routine vaccinations including OPV. There was no statistically significant difference between the 2-dose (10, 14 weeks of age) and 3-dose (6, 10, 14 weeks of age) groups in terms of anti-rotavirus IgA seroconversion rates.

Rationale

Continuing evaluation of the HRV vaccine in Africa, this study will evaluate the efficacy, safety and immunogenicity of the HRV vaccine at the selected optimum virus concentration in healthy African infants when given concomitantly with routine Expanded Program of Immunisation (EPI) vaccines. (Amendment 1: 24 August 2005) Study rota-013 did not indicate any difference in immunogenicity between the 2-dose and 3-dose groups but study rota-014 indicated that 2 doses at 10 and 14 weeks of age were better than two doses at 6 and 10 weeks of age. In both studies, the anti-rotavirus IgA seroconversion rate was in the range of 36%-61% after two doses (given at 10-14 weeks) or three doses. This study will evaluate efficacy of both the 2-dose (at 10 and 14 weeks of age) and 3-dose (at 6, 10 and 14 weeks of age) schedules. The viral concentration tested in study 013 ($10^{6.5}$ $CCID_{50}$) will be used. The main objective of this study is to evaluate the efficacy of the study vaccine to prevent severe rotavirus gastroenteritis (an episode of RV GE scored ≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) until one year of age. This study will also assess safety of the HRV vaccine relative to the placebo and immunogenicity in this study population.

Although this HRV vaccine is registered in Malawi and will become available in the private market; a placebo controlled trial is justified as the vaccine is not available through public health care programmes to the general population. More importantly as the vaccine is not yet recommended in the National Immunisation Guidelines, the data generated in this trial might facilitate evidence-based decisions on population-based vaccine utilisation in the country in particular and the region in general. (Malawi-specific Amendment 3: 22 February 2006)

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Objectives **Primary**

- To determine if the GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system[Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

Criteria: The primary objective will be reached if the lower limit of the of the 95% confidence interval (CI) on vaccine efficacy is >0%.

Secondary

Efficacy

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent any RV

GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- In South Africa, to assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

For subjects in Cohort 2 South Africa and the Cohort in Malawi:

- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7.
- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled

HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

(Amendment 6: 2 August 2007)

Safety

- In all subjects, to assess the safety of two or three doses of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations compared with placebo in terms of AEs leading to drop-out and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity

- In a subset of subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seropositivity rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after completion of the HRV vaccine course.

Definitions

- Diarrhoea: Passage of three or more looser than normal stools or watery stools within a day.
- Gastroenteritis (GE): Diarrhoea with or without vomiting.
- Rotavirus (RV) GE: An episode of GE occurring after administration of dose 1 of study vaccine in which RV other than vaccine strain is identified in a stool sample collected as soon as possible after the symptoms begin, and preferably not later than 7 days after the start of diarrhoea.
- Severe GE/RV GE: An episode of GE/RV GE scored ≥ 11 on the

20-point Vesikari scoring system [Ruuska, 1990].

- RV season in South Africa: Based on epidemiological observations, the RV season will be considered during the period from March 01 to July 31 in South Africa. (Amendment 2: 27 October 2005) (South Africa-specific Amendment 5: 10 July 2006)
- RV season in Malawi: The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. (Amendment 2: 27 October 2005)
- Efficacy follow-up period: Subjects in Cohort 1 South Africa will be followed until one year of age. Subjects in Cohort 2 South Africa will continue efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). (Amendment 6: 2 August 2007)

Study design

- Experimental design: Double-blind, randomised, placebo-controlled, multi-center, multi-country study with three parallel groups. (Amendment 2: 27 October 2005)
- Treatment Groups: (Amendment 1: 24 August 2005)
  - Group HRV 3-Dose: 3 doses of HRV given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N=1,600)
  - Group HRV 2-Dose: 2 doses of HRV given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose will be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding) (N=1,600))
  - Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N=1,600))

(Amendment 6: 2 August 2007)

- Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa. (South Africa-specific Amendment 5: 10 July 2006)

Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). Subjects who undergo initial HIV testing at Visit 4 will have one additional visit (Visit 5 at 21-48 days after Visit 4) to communicate

results of the initial HIV test to the parents/guardians. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling. For subjects in Cohort 2 South Africa, efficacy and safety follow-up will continue until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). For all subjects in Malawi, efficacy and safety follow-up will continue until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). These subjects will have an additional visit i.e. Visit 7. (Amendment 1: 24 August 2005) (Malawi-specific Amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=570; Not from cohort 2 in South Africa) and Dose 1 of HRV vaccine or placebo and routine EPI vaccines. Pre-test counselling, informed consent for HIV testing and blood sample from all subjects whose parent/guardian gave consent for HIV testing. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

Visit 2 (Month 1) – Dose 2 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (adverse events (AEs) leading to drop-out and SAEs). Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 1 and collection of an additional blood sample from subjects who test HIV positive at Visit 1 and are asymptomatic for a confirmatory HIV test. (South Africa-specific Amendment 5: 10 July 2006)

Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). Communication of HIV confirmatory test result and offer further counselling for subjects who had a HIV confirmatory test at Visit 2. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). If HIV test was not performed previously, offer pre-test counselling, informed consent for HIV testing and blood sample for HIV testing, if accepted. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

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Administrative Change 2

Visit 5 (Month 4) – At 21-48 days after Visit 4, only in subjects with initial HIV testing at Visit 4. Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 4. Collection of an additional blood sample from subjects who test HIV positive at Visit 4 and are asymptomatic for a confirmatory HIV test and planning for informing the parents/guardians about the confirmatory HIV test result in 2 week. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

Visit 6 (at one year of age) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) for subjects in Cohort 1 and 2 in South Africa and the Cohort in Malawi, and study conclusion for all subjects in Cohort 1 South Africa. A supplementary ICF will be provided to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed. A supplementary ICF will be provided to the parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi to request their child's/ward's participation in the second year follow-up for this study. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

Visit 7, only for subjects in Cohort 2 South Africa (at the end of the RV season in 2008 i.e. between 1 August 2008 and 15 September 2008) and for all subjects in the Cohort in Malawi (until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) and study conclusion. (Amendment 6: 2 August 2007)

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

- Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.
- Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.
- At subsequent visit/contact, inform parents/guardians of the confirmatory HIV test's results and offer further counselling.

– Results of HIV test conducted post-breast feeding cessation will be recorded in the CRF when consent to do so has been obtained from the subject's parents/guardians.

During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 in South Africa, and from Visit 1 up until Visit 7 for subjects in Cohort 2 South Africa), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa, HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics or hospitals as indicated as per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

- Treatment allocation: Randomised (1:1:1).
- Control: Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines. (The HRV placebo vaccine consists of all components of the study vaccine, i.e. excipient and buffer, but no RV particles).
- Blinding Double-blind.
- Vaccination schedule: Three-dose immunisation in healthy infants at approximately 6, 10, and 14 week of age.
- Hepatitis B, BCG and OPV vaccinations at birth are allowed according to the EPI schedule and their administration should be documented in the case report form (CRF). (Amendment 1: 24 August 2005)
- Routine EPI schedule vaccinations (DTPw-HB/Hib and OPV) should be administered concomitantly with the study vaccine at Visit 1, 2 and 3 following the EPI recommendation (at approximately 6, 10 and 14 weeks of age) and documented in the CRF. (Amendment 1: 24 August 2005)
- BCG at Visit 1 is allowed and should be documented in the CRF. (Amendment 1: 24 August 2005)
- All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF. (Amendment 1: 24 August 2005)
- No restrictions on feeding of infants before or after the administration of the study vaccine.
- Recording of height and weight at Visit 1, Visit 4, Visit 6 and Visit 7. (Amendment 1: 24 August 2005) (Amendment 6: 2

August 2007)

- Recording of AEs leading to drop out during the entire study period.
- Recording of SAEs during the entire study period.
- An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician monitors the safety aspects of all studies with the HRV vaccine. In that capacity, the IDMC will review each SAE reported during this study.
- Parents/guardians will be asked to contact the investigator or designated delegate in case of SAEs during the study period. Parents/guardians will be asked regarding occurrence of SAEs at each contact during the study (at planned study visits as well as any visit/contact by the study staff).
- Blood samples will be collected from a subset of subjects (N=570 subjects; not from subjects in cohort 2 in South Africa) at Visit 1 and from all subjects at Visit 4 to measure anti-rotavirus IgA antibodies. (South Africa-specific Amendment 5: 10 July 2006)
- Blood sample will be collected from all subjects whose parent/guardian gave prior consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at the subsequent visit from subjects who test HIV positive at the initial test and are asymptomatic. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Active follow-up for occurrence of GE episodes (diarrhoea) via weekly visit to a subject by study personnel during the entire study period (from the day of Dose 1 until Visit 6 for subjects in Cohort 1 South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi). (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

Study staff will visit the subject every week to check for occurrence of any diarrhoea during the entire study period.

Parents/guardians of study subjects will be instructed to contact the study staff in case of diarrhoea.

The study staff will direct the parents/guardians to the nearest hospital/medical facility as necessary.

For each diarrhoea episode, a GE diary card should be completed daily until end of diarrhoea.

- During each GE episode, a stool sample(s) should be collected as soon as possible after the symptoms begin, and preferably not later than 7 days after the start of diarrhoea.

- Two occurrences of GE should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.
- Results of HIV testing on blood samples collected after informed consent for HIV testing has been obtained will be communicated to the parents/guardians at the subsequent visit/contact. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive at the initial test and are asymptomatic, a confirmatory HIV test should be performed at the subsequent visit. If an initial HIV test is done at Visit 4, there will be an additional study visit (Visit 5 21-48 days after Visit 4) so that the study staff can inform parents/guardians of HIV test results and offer post-test counselling. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

  In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [South African National Department of Health Guidelines for the Management of HIV-infected Children 2005] and Standard of Care provided during GSK sponsored trials. (South Africa-specific Amendment 5: 10 July 2006)

  In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi (1st edition October 2003 or later edition)] and Standard of Care provided during GSK sponsored trials. (Amendment 2: 27 October 2005) (Malawi-specific Amendment 3: 22 February 2006)

- The study staff will, where clinically indicated and/or for hospitalised HIV positive children, facilitate access of study subjects to a HIV staging facility and/or ARV treatment centers during the study, but decisions towards treatment will be taken by appropriate staff at these treatment centers. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- In Malawi, the study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health. (Malawi-specific amendment 4: 15 May 2006)

- In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or Prevention of Mother To Child Transmission (PMTCT) programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed (due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed. (South Africa-specific Amendment 5: 10 July 2006)
- Data collection: CRF. (Amendment 1: 24 August 2005)
- Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period. Results of the analysis for efficacy and safety data collected during the second efficacy follow-up period will be provided in an annex report (Amendment 6: 2 August 2007).
- An interim analysis on vaccine efficacy against severe RV GE and any RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007.The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. (Amendment 6: 2 August 2007)
- Duration of the study: The study subjects in Cohort 1 in South Africa will be followed until one year of age, and the intended duration of the study, per subject, will not exceed a maximum of 10 to 11 months. The study subjects in Cohort 2 South Africa will be followed until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008), and the intended duration of the study, per subject, will not exceed a maximum of 24 months. The study subjects in the Cohort in Malawi will be followed until at least 18 months of age and not more than two

years of age (last subject last visit not later than 30 January 2009) and the study duration will not exceed a maximum of 24 months (Amendment 6: 2 August 2007).

Number of subjects

Total target enrolment will be 4,800 subjects (1,600 subjects in each group). (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007).

All enrolled subjects will be followed for efficacy and safety. The subjects in Cohort 1 in South Africa will be followed for efficacy and safety until one year of age. The subjects in Cohort 2 South Africa will be followed for efficacy and safety until the end of the 2008 RV season (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). (Amendment 6: 2 August 2007)

A subset of 570 subjects will provide a blood sample at Visit 1 and all subjects will provide a blood sample at Visit 4 to measure anti-rotavirus IgA antibodies (Amendment 1: 24 August 2005). No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1. (South Africa-specific Amendment 5: 10 July 2006)

Blood sample from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at the subsequent visit from subjects who test HIV positive after the initial test and are asymptomatic. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Primary endpoint

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

Secondary endpoints

Efficacy

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 6. (Amendment 1: 24 August 2005)
- In South Africa, occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

For subjects in Cohort 2 South Africa and the Cohort in Malawi:

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or

placebo until Visit 7, and from Visit 6 to Visit 7.

- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

(Amendment 6: 2 August 2007)

Safety

- For all subjects, occurrence of AEs/SAEs leading to drop-out throughout the entire study period.
- For all subjects, occurrence of SAEs throughout the entire study period.

Immunogenicity

- In a subset of subjects, seroconversion rate and Geometric Mean concentration (GMC) to anti-rotavirus IgA antibody at Visit 4.
- In all subjects, seropositivity rate and GMC to anti-rotavirus IgA antibody at Visit 4.

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List of Abbreviations

AE	Adverse event
ARV	Anti-retroviral
ATP	According to Protocol
BCG	Bacille Calmette-Guérin
CI	Confidence Interval
CRF	Case Report Form (Amendment 1: 24 August 2005)
CSC	Central Study Coordinator
DMEM	Dulbecco's Modified Eagle Medium
ELISA	Enzyme Linked Immunosorbent Assay
EPI	Expanded Program of Immunisation
ffu	Foci Forming units
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HRV	Human Rotavirus
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IPV	Inactivated Poliovirus Vaccine
IRB	Institutional Review Board

IS	Intussusception
MedDRA	Medical Dictionary for Regulatory Activities
OPV	Oral Poliovirus Vaccine
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother To Child Transmission (South Africa-specific Amendment 5: 10 July 2006)
RV	Rotavirus
RVP	Rotavirus Vaccine Program (Amendment 6: 2 August 2007)
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
USA	United States of America

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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. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the study personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double blind. Partially blind is to be used for study designs with different blinding levels between different groups, e.g. double blinded consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event.

Central Study Co-ordinator: An individual assigned by and centrally located at GSK Biologicals at Rixensart who is responsible for assuring proper conduct of a clinical study.

Diarrhoea: Passage of three or more looser than normal stools or watery stools within a day.

Efficacy follow-up period: Subjects in Cohort 1 South Africa will be followed until one year of age. Subjects in Cohort 2 South Africa will continue efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue

	efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). (Amendment 6: 2 August 2007)
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 (GE):	Diarrhoea with or without vomiting.
Independent Data Monitoring Committee (IDMC):	The IDMC is responsible for safety monitoring during the rotavirus vaccine trials taking into account the potential benefits of the vaccine in different parts of the world.
Investigational product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.
Protocol amendment:	ICH defines a protocol amendment as: "A written description of a change(s) to or formal clarification of a protocol." GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.

Randomisation:	Process of random attribution of treatment to subjects in order to reduce bias of selection
Regurgitate:	Effortless emesis of swallowed contents.
Rotavirus (RV) GE caused by the circulating wild-type rotavirus strain: (Amendment 1: 24 August 2005)	An episode of gastroenteritis occurring after administration of dose 1 of study vaccine in which rotavirus other than vaccine strain is identified in a stool sample collected as soon as possible after the symptoms begin, and preferably not later than 7 days after the start of diarrhoea.
RV season in South Africa: (Amendment 1: 24 August 2005)	Based on epidemiological observations in South Africa, the RV season will be considered during the period from March 01 to July 31.
RV season in Malawi:	The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. (Amendment 2: 27 October 2005)
Separate episodes of GE:	Two occurrences of GE symptoms with 5 or more diarrhoea-free days between the episodes.
Serious Adverse Event (SAE):	Any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, an important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition i.e intussusception.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) seronegative for anti-rotavirus IgA antibodies.
Seronegative:	A subject whose antibody concentration was below the assay cut-off value.
Seropositive:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Severe GE/RV GE:	An episode of GE/RV GE scored ≥ 11 on the 20-point

Vesikari scoring system [Ruuska, 1990].

Site Monitor: An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Study Monitor: An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.

Subject: Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.

Subject number: A unique number identifying a subject, assigned to Each subject consenting to participate in the study.

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.

Treatment number: An unique number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

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

1. INTRODUCTION

1.1. Background

Rotavirus (RV) is the most important cause of severe gastroenteritis (GE) requiring hospitalisation of infants and young children in developed countries, and is a frequent cause of death in children less than 5 years of age in developing regions of the world. A recent review estimates that 611,000 (range 454,000–705,000) RV-related deaths occur in children under 5 years of age annually [Parashar, 2006]. From 2000 to 2004, RV was estimated to cause 39% of hospitalisations for childhood diarrhoea. (Malawi-specific Amendment 3: 22 February 2006) The majority of RV related deaths occur in Africa, Indian subcontinent and Latin America. In South Africa and all subsaharan countries, RV is a large health burden in young children accounting for approximately 25% of the diarrhoeal deaths reported. RV is responsible for approximately 25% of all hospitalisations due to diarrhoeal diseases in young children under five years in South Africa [Cunliffe , 1998; Steele , 2003]. In South Africa, the disease was shown to be seasonal with a clear peak in autumn winter season [Steele , 2003]. In Malawi, RV is responsible for a third of outpatient attendances and hospital admissions for acute GE among children under 5 years of age [Cunliffe, 2001]. More than 80% of RV GE cases occur in infants less than one year of age. In Malawi, RV is identified throughout the year; diarrhoeal disease of all causes is most common during the warm, rainy season (November-March), but the proportion of diarrhoeal episodes attributed to RV is greatest during the cooler, dry season (May-September) [Cunliffe 2001 thesis]. The impact of RV season in Malawi is minimal. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. Recently, the greater diversity of RV serotypes in some African countries has been recognised. In particular, serotypes G8 and P[6] have been documented in multiple settings, and in Malawi serotype G8 has comprised approximately 30% of all RV serotypes [Cunliffe, 1999; Cunliffe, 2001]. It was estimated that an effective vaccine against RV could prevent 16% of all diarrhoeal deaths in children below 5 years of age [De Zoysa, 1985]. (Amendment 2: 27 October 2005)

The significant global health burden due to RV disease in both developed and developing countries prompted the development of RV vaccines. Prevention by vaccination is considered to be critical for effective control of RV infection since only non-specific symptomatic therapies are available. One vaccine, Rotashield®, a tetravalent rhesus human reassortant RV vaccine, was licensed by Wyeth-Lederle in the United States in 1998 but was withdrawn from the market in 1999 due to an increased risk of intussusception (IS) (telescoping of the intestine) shortly after its administration.

GlaxoSmithKline (GSK) Biologicals has developed a monovalent vaccine based on the human rotavirus (HRV) strain 89-12 belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old infant with a mild RV diarrhoea in Cincinnati, United States. The candidate vaccine with the parent 89-12 vaccine was well-tolerated, immunogenic and effective in preventing RV GE among vaccinated infants during trials in the United States [Bernstein, 1999; Bernstein, 2002; Bernstein, 1998]. GSK Biologicals has implemented several process changes to the 89-12 vaccine

candidate to develop a lyophilised HRV vaccine containing RIX4414 HRV vaccine strain (cloned 89-12 HRV strain at passage 43) for oral administration after reconstitution with the supplied diluent.

Clinical results of the GSK Biologicals HRV vaccine

GSK Biologicals' HRV vaccine has been tested in Phase I-III clinical studies conducted in Asia, Africa, Europe, Latin America and North America. The HRV vaccine is registered in Mexico since July 2004.

In all studies adults, previously infected children (1-3 years old) and infants, the HRV vaccine was well-tolerated with side effects similar to the placebo.

The HRV vaccine was efficacious in protecting infants against RV GE in two phase II efficacy trials completed so far.

In Finland (Study rota-004), 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) 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-HB] 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 for the pooled HRV vaccine groups was 78.1% (95% CI: -91.1; 98.2) for the second year efficacy follow-up and 74.7% (95% CI: 37.7; 90.1) for the combined efficacy follow-up periods.

Two phase II trials have been conducted in South Africa and the results are summarised here. In the first phase II trial in South Africa (study rota-014), two doses of HRV vaccine ($10^{5.2}$ ffu) were administered at 6 and 10 weeks (first study part) or 10 and 14 weeks of age (second study part) concomitantly with oral polio vaccine (OPV) or inactivated polio vaccine (IPV). The objective of this study was to see if HRV vaccine would interfere with the take of OPV. The results of this study demonstrated that immune response to the OPV vaccine did not seem to be affected by co-administration with HRV vaccine. There was an interference of OPV on HRV immunogenicity after the first dose of HRV vaccine but not after the second dose. Anti-rotavirus IgA antibody seroconversion rate was higher when two doses were given at 10 and 14 weeks of age compared to two doses given at 6 and 10 weeks of age. In the next phase II study (study rota-013) in South Africa, two doses of HRV vaccine ($10^{6.5}$ $CCID_{50}$) administered at 10

and 14 weeks were compared with three doses administered at 6, 10 and 14 weeks of age when given concomitantly with routine vaccinations including OPV. There was no statistically significant difference between the 2-dose (10, 14 weeks of age) and 3-dose (6, 10, 14 weeks of age) groups in terms of anti-rotavirus IgA seroconversion rates. In both studies, the anti-rotavirus IgA seroconversion rate was in the range of 36%-61% after two or three doses.

In rota-014 first study part (N=271), all infants were enrolled regardless of their human immunodeficiency virus (HIV) status of the mother. A cluster of fatalities was observed within a few months after immunisation. Six fatality cases were diagnosed to be due to the HIV status of the infants. Among these 6, 4 were in the placebo group and 2 in the vaccine group. An Independent Data Monitoring Committee (IDMC) that monitors the safety aspects in all trials during the HRV vaccine clinical development requested that the study rota-014 be put on hold and re-started with inclusion of babies whose mothers tested HIV negative. The second study part (after the 2002 RV season) was done with screening of the mothers and inclusion of babies whose mothers tested HIV negative. A third study (rota-022) in South Africa has started in April 2005. This study will evaluate the safety, reactogenicity and immunogenicity of three doses of HRV vaccine in HIV positive infants. This study will be closely monitored by the IDMC. In case of safety concern, the IDMC may recommend that study Rota-022 be put on hold. In this event, the current protocol would be amended to only include HIV negative infants. Also see letter on WHO's position on use of live vaccines addressed to the Medicines Control Council on September 26, 2004 by Professor [redacted] WHO officer provided in Annex 1. The 2004 annual antenatal survey indicated that HIV prevalence among pregnant women is 29.5% (CI 28.5% - 30.5%) compared to the 27.9% (CI 26.8% - 28.9%) observed in 2003 [Department of Health, South Africa, 2004]. (Amendment 1: 24 August 2005)

An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development. All reported serious adverse events (SAEs) unblinded by treatment group are periodically reviewed by the IDMC. As of 15 July 2005, the safety database for GSK Biologicals' HRV vaccine contains 89,243 subjects. Up to 15 July 2005, 5,782 subjects have reported a total of 6,872 SAEs. Of these, a total of 67 SAEs have been considered as possibly related by the investigators or with unknown relationship. (Amendment 2: 27 October 2005)

In view of the history of Rotashield® as discussed above, IS is a particular point of interest in the safety evaluation. A large phase III multi-country trial rota-023 involving 63 225 infants was undertaken in 11 countries in Latin America and in Finland with the primary objective of assessing the safety of the HRV vaccine in terms of occurrence of definite IS. Definite IS required the diagnosis of IS to be confirmed on the demonstration of invagination of the intestine at surgery or autopsy, or by using radiologic techniques: gas/liquid contrast enema or abdominal ultrasound. The primary safety evaluation was based on occurrence of definite IS during 31 days (Day 0 to Day 30) after each vaccine dose. The rationale for focussing on the critical risk window of 31 days after vaccination was based on the consideration that vaccination-related IS would occur when the vaccine virus replication and host responses are maximal.

Final statistical analysis of safety from Dose 1 until Visit 3 (median follow-up duration: 100 days) was performed for the entire study cohort. A total of 13 definite IS cases (6 in the HRV vaccine group and 7 in the placebo group) were diagnosed within 31 days (Day 0 to Day 30) after any dose of vaccine. 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 after any dose [O'Ryan, 2004]. Similarly, there was no increased risk for IS after Dose 1 or Dose 2 versus placebo. The observed point estimate is below the Risk Difference, which was initially communicated for Rotashield™ (4/10,000) and which led to the withdrawal of Rotashield™ in the USA in 1999 [Murphy, 2001; Kramarz, 2001]. It is also below the Risk Difference which was ultimately published as the 'consensus estimate' for the risk increase of Rotashield™ (based on subsequently performed epidemiological studies, i.e. 1/10,000) [Murphy , 2003; Peter, 2002]. Also, there was no statistically significant increase in the percentage of subjects reporting definite IS diagnosed from Dose 1 up to Visit 3 in the HRV vaccine group compared to the Placebo group (secondary safety endpoint). The Relative Risk for definite IS diagnosed from Dose 1 up to Visit 3 was 0.56 (95% CI: 0.25; 1.24). Finally, when comparing the occurrence of the IS following Rotashield™ which was withdrawn from market and GSK Biologicals' HRV vaccine candidate, the clear difference in the profile of those two vaccine is evident. In study 023, most of the IS cases occurred at 4-5 months of age which is close to the peak incidence of IS and were not clustered in any period after vaccination. In contrast, IS cases following Rotashield™ vaccination were clustered in the 3 to 7 day period after vaccination and most were observed post Dose 1 [Murphy, 2001]. Further, in study Rota 023 there was no evidence for a clinically meaningful difference between groups for SAEs, related SAEs, deaths, or SAEs and non-serious adverse events (AEs) leading to drop-out from Dose 1 until Visit 3.

A subset of 20,169 subjects from study rota-023 were followed for efficacy against severe RV GE (defined as an episode that required hospitalisation and/or re-hydration therapy (equivalent to WHO plan B or C) in a medical facility). Efficacy follow-up until one year of age was recently completed and significant efficacy against severe RV GE was established. Vaccine efficacy against severe RV GE caused by the circulating wild-type RV was 84.7% (95% CI: 71.7; 92.4). Significant protection was shown against G1 and non-G1 serotypes.

Please refer to the latest version of the investigator brochure (Edition 8) for a detailed review of other information on the HRV vaccine. (Amendment 6: 2 August 2007)

1.2. Rationale for the study

Continuing evaluation of the HRV vaccine in Africa, this study will evaluate the efficacy, safety and immunogenicity of the HRV vaccine at the selected optimum virus concentration in healthy African infants when given concomitantly with routine Expanded Program of Immunisation (EPI) vaccines. (Amendment 1: 24 August 2005) Study rota-013 did not indicate any difference in immunogenicity between the 2-dose and 3-dose groups but study rota-014 indicated that 2 doses at 10 and 14 weeks of age were better than two doses of 6 and 10 weeks of age. In both studies, the anti-rotavirus IgA seroconversion rate was in the range of 36%-61% after two or three doses. This study

will evaluate efficacy of both the 2-dose (at 10 and 14 weeks of age) and 3-dose (at 6, 10 and 14 weeks of age) schedules. The same viral concentration tested in study 013 ($10^{6.5}$ CCID50) will be used. The main objective of this study is to evaluate the efficacy of the study vaccine to prevent severe rotavirus gastroenteritis (an episode of RV GE scored ≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) until one year of age. This study will also assess safety of the HRV vaccine relative to the placebo and immunogenicity in this study population.

Although this HRV vaccine is registered in Malawi and South Africa, and will become available in the private market; a placebo controlled trial is justified as the vaccine is not available through public health care programmes to the general population. More importantly as the vaccine is not yet recommended in the National Immunisation Guidelines, the data generated in this trial might facilitate evidence-based decisions on population-based vaccine utilisation in the country in particular and the region in general. (Malawi-specific Amendment 3: 22 February 2006) (Amendment 6: 2 August 2007)

2. OBJECTIVES

2.1. Primary objective

- To determine if the GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005).

Criteria: The primary objective will be reached if the lower limit of the of the 95% CI on vaccine efficacy is >0%.

Refer to Section 10.1 for definition of the primary endpoint.

2.2. Secondary objectives

Efficacy

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- In South Africa, to assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

For subjects in Cohort 2 South Africa and the cohort in Malawi:

- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7.
- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

(Amendment 6: 2 August 2007)

Safety

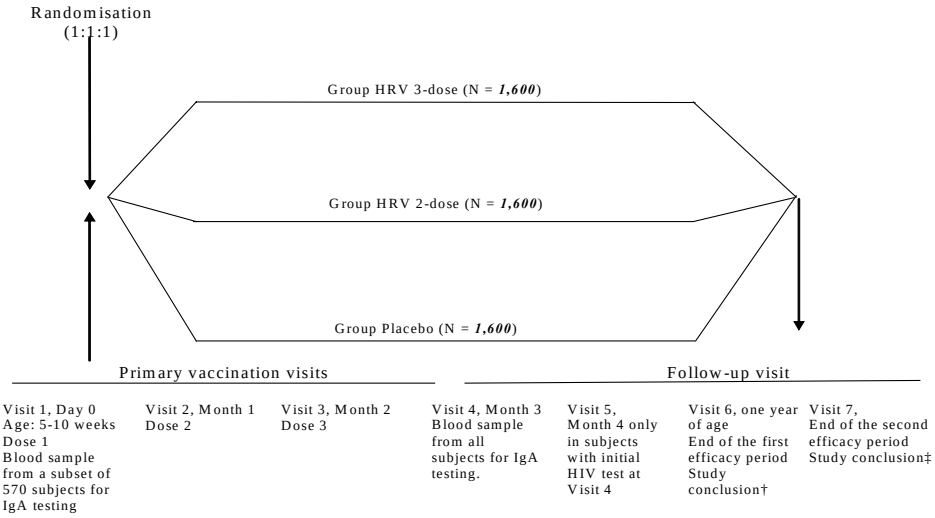
- In all subjects, to assess the safety of two or three doses of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations compared with placebo in terms of AEs leading to drop-out and SAEs during the entire course of the study.

Immunogenicity

- In a subset of subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seroconversion rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of anti-rotavirus IgA antibody seropositivity rate one month after completion of the HRV vaccine course.
- In all subjects, to assess the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after completion of the HRV vaccine course.

Refer to Section 10.2 for definition of the secondary endpoints.

3. STUDY DESIGN OVERVIEW



Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Blood sample to be collected from all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample at the subsequent visit from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
† For subjects in Cohort 1 South Africa (Amendment 6: 2 August 2007)
‡ For subjects in Cohort 2 South Africa and the Cohort in Malawi (Amendment 6: 2 August 2007)

- Experimental design: Double-blind, randomised, placebo- controlled, multi-center, multi-country study with three parallel groups. (Amendment 2: 27 October 2005)
- Treatment Groups:
  - Group HRV 3-Dose: 3 doses of HRV given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N = 1,600)
  - Group HRV 2-Dose: 2 doses of HRV given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose will be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding) (N = 1,600)
  - Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N = 1,600)

(Amendment 6: 2 August 2007)

- Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa. (South Africa-specific Amendment 5: 10 July 2006)

- Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). Subjects who undergo initial HIV testing at Visit 4 will have one additional visit (Visit 5 at 21-48 days after Visit 4) to communicate results of the initial HIV test to the parents/guardians. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling. For subjects in Cohort 2 South Africa, efficacy and safety follow-up will continue until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). For all subjects in Malawi, efficacy and safety follow-up will continue until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). These subjects will have an additional visit i.e. Visit 7. (Amendment 1: 24 August 2005) (Malawi-specific Amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)
  - Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=570 Not from cohort 2 in South Africa) and Dose 1 of HRV vaccine or placebo and routine EPI vaccines. Pre-test counselling, informed consent for HIV testing and blood sample from all subjects whose parent/guardian gave consent for HIV testing. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)
  - Visit 2 (Month 1) – Dose 2 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (adverse events (AEs) leading to drop-out and SAEs). Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 1 and collection of an additional blood sample from subjects who test HIV positive at Visit 1 and are asymptomatic for a confirmatory HIV test. (South Africa-specific Amendment 5: 10 July 2006)
  - Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). Communication of HIV confirmatory test result and offer further counselling for subjects who had a HIV confirmatory test at Visit 2. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)
  - Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). If HIV test was not performed previously, offer pre-test counselling, informed consent for HIV testing and blood sample for HIV testing, if accepted. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)
  - Visit 5 (Month 4) – At 21-48 days after Visit 4. Only for subjects with initial HIV test performed at Visit 4. Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 4. Collection of an additional blood sample from subjects who test HIV positive at Visit 4 and are asymptomatic for a confirmatory HIV test and planning for

informing the parents/guardians about the confirmatory HIV test result in 2 weeks. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

– Visit 6 (at one year of age) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) for subjects in Cohort 1 and 2 in South Africa and the Cohort in Malawi and study conclusion for all subjects in Cohort 1 South Africa. A supplementary ICF will be provided to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed. A supplementary ICF will be provided to the parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi to request their child's/ward's participation in the second year follow-up for this study. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

– Visit 7, only for subjects in Cohort 2 South Africa (at the end of the RV season in 2008 i.e. between 1 August 2008 and 15 September 2008) and for all subjects in the Cohort in Malawi (until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) and study conclusion. (Amendment 6: 2 August 2007)

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

- Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.
- Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.
- At subsequent visit/contact, inform parents/guardians of the confirmatory HIV test's results and offer further counselling.
- Results of HIV test conducted post-breast feeding cessation will be recorded in the CRF when consent to do so has been obtained from the subject's parents/guardians.

During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 in South Africa, and from Visit 1 up until Visit 7 for subjects in Cohort 2 South Africa), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa, HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics or hospitals, as indicated as per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

- Treatment allocation: Randomised (1:1:1).
- Control: Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines. (The HRV placebo vaccine consists of all components of the study vaccine, i.e. excipient and buffer, but no RV particles).
- Blinding Double-blind.
- Vaccination schedule: Three-dose immunisation in healthy infants at approximately 6, 10, and 14 week of age.
- Hepatitis B, BCG and OPV vaccinations at birth are allowed according to the EPI schedule and their administration should be documented in the case report form (CRF). (Amendment 1: 24 August 2005)
- Routine EPI schedule vaccinations (DTPw-HB/Hib and OPV) should be administered concomitantly with the study vaccine at Visit 1, 2 and 3 following the EPI recommendation (at approximately 6, 10 and 14 weeks of age) and documented in the CRF. (Amendment 1: 24 August 2005)
- BCG at Visit 1 is allowed and should be documented in the CRF. (Amendment 1: 24 August 2005)
- All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF. (Amendment 1: 24 August 2005)
- No restrictions on feeding of infants before or after the administration of the study vaccine.
- Recording of height and weight at Visit 1, Visit 4, Visit 6 and Visit 7. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)
- Recording of AEs leading to drop out during the entire study period.
- Recording of SAEs during the entire study period.
- An Independent Data Monitoring Committee (IDMC) consisting of clinical experts and a biostatistician monitors the safety aspects of all studies with the HRV vaccine. In that capacity, the IDMC will review each SAE reported during this study.
- Parents/guardians will be asked to contact the investigator or designated delegate in case of SAEs during the study period. Parents/guardians will be asked regarding occurrence of SAEs at each contact during the study (at planned study visits as well as any visit/contact by the study staff).
- Blood samples will be collected from a subset of subjects (N=570 subjects; not from subjects in cohort 2 in South Africa) at Visit 1 and from all subjects at Visit 4 to measure anti-rotavirus IgA antibodies. (South Africa-specific Amendment 5: 10 July 2006)
- Blood sample will be collected from all subjects whose parent/guardian gave prior consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at the subsequent visit from subjects who test HIV positive at the initial test and are asymptomatic. (Amendment 1: 24 August 2005) (Malawi-

specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

- Active follow-up for occurrence of GE episodes (diarrhoea) via weekly visit to a subject by study personnel during the entire study period (from the day of Dose 1 until Visit 6 for subjects in Cohort 1 South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi). (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

Study staff will visit the subject every week to check for occurrence of any diarrhoea during the entire study period.

Parents/guardians of study subjects will be instructed to contact the study staff in case of diarrhoea.

The study staff will direct the parents/guardians to the nearest hospital/medical facility as necessary.

For each diarrhoea episode, a GE diary card should be completed daily until end of diarrhoea.

- During each GE episode, a stool sample(s) should be collected as soon as possible after the symptoms begin, and preferably not later than 7 days after the start of diarrhoea.

Two occurrences of GE should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.

Results of HIV testing on blood samples collected after informed consent for HIV testing has been obtained will be communicated to the parents/guardians at the subsequent visit/contact. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive at the initial test and are asymptomatic, a confirmatory HIV test should be performed at the subsequent visit. If an initial HIV test is done at Visit 4, there will be an additional study visit (Visit 5 21-48 days after Visit 4) so that the study staff can inform parents/guardians of HIV test results and offer post-test counselling. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [South African National Department of Health Guidelines for the Management of HIV-infected Children 2005] and Standard of Care provided during GSK sponsored trials. (South Africa-specific Amendment 5: 10 July 2006).

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy

in Malawi (1st edition October 2003 or later edition)] and Standard of Care provided during GSK sponsored trials. (Amendment 2: 27 October 2005) (Malawi-specific Amendment 3: 22 February 2006)

The study staff will, where clinically indicated and/or for hospitalised HIV positive children, facilitate access of study subjects to a HIV staging facility and/or ARV treatment centers during the study, but decisions towards treatment will be taken by appropriate staff at these treatment centers. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

- In Malawi, the study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health. (Malawi-specific amendment 4: 15 May 2006)
- In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed (due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed. (South Africa-specific Amendment 5: 10 July 2006)
- Data collection: CRF. (Amendment 1: 24 August 2005)
- Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period. Results of the analysis for efficacy and safety data collected during the second efficacy follow-up period will be provided in an annex report. (Amendment 6: 2 August 2007)
- An interim analysis on vaccine efficacy against both severe and any RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. (Amendment 6: 2 August 2007)

- Duration of the study: The study subjects in Cohort 1 in South Africa will be followed until one year of age, and the intended duration of the study, per subject, will not exceed a maximum of 10 to 11 months. The study subjects in Cohort 2 South Africa will be followed until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008), and the intended duration of the study, per subject, will not exceed a maximum of 24 months. The study subjects in the Cohort in Malawi will be followed until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) and the study duration will not exceed a maximum of 24 months (Amendment 6: 2 August 2007)

4. STUDY COHORT

4.1. Number of subjects / centres

Total target enrolment will be 4,800 subjects (1,600 subjects in each group). (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007). Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

All subjects will be enrolled at multiple sites in Africa.

As of January 2006 a total of 1,827 subjects have been enrolled in South Africa (Cohort 1 in South Africa). Enrolment in South Africa was suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa shall resume after the RV season to enrol the total planned number of subjects (Cohort 2 in South Africa). (South Africa-specific Amendment 5: 10 July 2006)

All enrolled subjects will be followed for efficacy and safety. The subjects in Cohort 1 in South Africa will be followed for efficacy and safety until one year of age. The subjects in Cohort 2 South Africa will be followed for efficacy and safety until the end of the 2008 RV season (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). (Amendment 6: 2 August 2007).

A subset of 570 subjects will provide a blood sample at Visit 1 to measure anti-rotavirus IgA antibodies. All subjects will provide a blood sample at Visit 4 to assess the immunogenicity of study vaccines (anti-rotavirus IgA antibodies) (Amendment 1: 24 August 2005). No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1. (South Africa-specific Amendment 5: 10 July 2006)

Blood sample from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at the subsequent visit from subjects who test HIV positive after the initial test and are asymptomatic. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Refer to Appendix C for a summary of the recruitment plan.

4.2. Inclusion criteria

All subjects must satisfy the following criteria at study entry:

- Subjects who the investigator believes that their parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits) should be enrolled in the study.
- A male or female child between, and including, 5 and 10 weeks of age at the time of the first study vaccination.
- Written informed consent obtained from the parent or guardian of the subject who is of legal age (i.e. parent/guardian should be 18 years or older). (South Africa-specific Amendment 5: 10 July 2006)
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- In South Africa, birth weight > 2000 g or if weight unknown, gestation period > 36 weeks. (South Africa-specific Amendment 5: 10 July 2006)

4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If any apply, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- 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).
- Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)
- History of use of experimental rotavirus vaccine.
- Previous routine vaccination except BCG, HBV and OPV vaccination at birth (should be documented in the CRF). (Amendment 1: 24 August 2005)
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

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- Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5°C (99.5°F) / Axillary temperature <37.5°C (99.5°F) / Rectal temperature <38°C (100.4°F).) (warrants deferral of vaccination).
- Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).
- Previous confirmed occurrence of RV GE.
- A family history of congenital or hereditary immunodeficiency.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- History of any neurologic disorders or seizures.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

4.4. Elimination criteria during the study

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol (ATP) analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
- Administration of immunoglobulins and/or any blood products during the study period.

4.5. Contraindications to subsequent vaccination

GSK Biologicals' HRV vaccine or its placebo

The following AEs constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any AE:

- Hypersensitivity reaction due to the vaccine.

- IS.

The following AEs constitute contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.4), or withdrawn at the discretion of the investigator (see Section 9). The subject must be followed until resolution of the event, as with any AE (see Section 8.7).

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

5. CONDUCT OF STUDY

5.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the 2004 Declaration of Helsinki (Protocol Appendix A) and local rules and regulations of the country. (Administrative change 1: 22 September 2005)

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, submission to the local regulatory authority may not be required. When submission to the local regulatory authority is required, the timing of the submission relative to IEC/IRB submission or approval and whether or not the authority will provide their approval of or favourable opinion on the protocol or amendment before it can be implemented will depend on local regulatory requirements.

5.1.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonised Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

- At least five members.
- At least one member whose primary area of interest is in a non-scientific area.
- At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator. A list of the professions of the IRB/IEC members should be obtained by GSK Biologicals' Study Monitor/ Site Monitor/ investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures and information about payments and compensation available to subjects, will be submitted to the IRB/IEC by the investigator. Written and dated unconditional approval/favourable opinion from the IRB/IEC of the protocol and amendment (if any), written informed consent form, consent form updates (if any and applicable), subject recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to subjects must be in the possession of the investigator and GSK before commencement of the study. This approval/favourable opinion must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals' data will be supplied by the investigator to the hospital/ university/ independent IRB/IEC for review and approval of the protocol. Verification of the unconditional approval/favourable opinion of the IRB/IEC will be transmitted by the investigator to GSK Biologicals' Study Monitor prior to shipment of vaccine supplies and CRFs to the site. (Amendment 1: 24 August 2005)

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval/ favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or where permitted by all applicable regulatory requirements or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor[s], telephone number[s].) Administrative changes and amendments not submitted for approval are submitted to the IRB/IEC for information only. However, written verification that such documents were submitted should be obtained. Approvals/ verifications must be transmitted in writing to GSK Biologicals' Study Monitor by the investigator.

The IRB/IEC must be informed by the investigator of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,
- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the subjects or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination (see Appendix B for further details).

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5.1.2. Informed consent

Freely given informed consent should be obtained from every subject's parents/guardians prior to clinical trial participation.

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

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the 2004 Declaration of Helsinki. (Administrative change 1: 22 September 2005) Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to the subjects' parents/guardians.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential subjects' parents/guardians face to face. At the request of the [redacted], potential subjects' parents/guardians will receive a summary document with the gist of the Informed Consent Form to aid comprehension. (Administrative change 1: 22 September 2005) The Informed Consent Form may be read to the subjects' parents/guardians, but, in any event, the investigator or designate shall give the subjects' parents/guardians ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

Informed Consent Form must be in a language fully comprehensible to the prospective subjects' parents/guardians. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the parents/guardians and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. All illiterate individuals will have the study, the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the parents'/guardians' incapacity precludes this and provided that the local legal obligations are fulfilled.

At the request of the [redacted], all parents/guardians will have to complete an Informed Consent Feedback Form. The responses of the parents/guardians to the questions in the Informed Consent Feedback Form will allow the person taking informed consent to understand what has or has not been understood by the subjects' parents/guardians. In case of incorrect responses, the informed consent will be explained again to the parents/guardians and the investigator or his delegate will assess comprehension. Responses from parents/guardians of the first 50 subjects will be transmitted to the [redacted]. (Administrative change 1: 22 September 2005)

Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or GSK Biologicals' professional and Regulatory Compliance persons. The parents/guardians should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects' parents/guardians, and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to subjects' parents/guardians.

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

a. That the trial involves research.
b. The purpose of the trial.
c. The trial treatment(s) and the probability for random assignment to each treatment.
d. The trial procedures to be followed, including all invasive procedures.
e. The subject's parents'/guardians' responsibilities.
f. Those aspects of the trial that are experimental.
g. The reasonably foreseeable risks or inconveniences to the subjects and, when applicable, to an embryo, fetus or nursing infant.
h. The reasonable expected benefits. When there is no intended clinical benefit to subjects, the subjects' parents/guardians should be made aware of this.
i. The alternative procedure(s) or course(s) of treatment/ methods of prevention that may be available to subjects, and their important potential benefits and risks.
j. The compensation and/or treatment available to subjects in the event of trial-related injury.
k. The anticipated prorated payment, if any, to subjects' parents/guardians for participating in the trial.
l. The anticipated expenses, if any, to subjects' parents/guardians for participating in the trial.
m. That the subjects' participation in the trial is voluntary and subjects' parents/guardians may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which subjects are otherwise entitled.
n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of subjects, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the subject's parents/guardians is authorising such access.
o. That records identifying subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly

available. If the results of the trial are published, subjects' identity will remain confidential.

p. That the subjects' parents/guardians will be informed in a timely manner if information becomes available that may be relevant to the subjects' parents/guardians willingness for continued participation in the trial.

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

r. The foreseeable circumstances and/or reasons under which a subject's participation in the trial may be terminated.

s. The expected duration of a subject's participation in the trial.

t. The approximate number of subjects involved in the trial.

GSK Biologicals will prepare a model Informed Consent Form which will embody all the elements described above. While it is strongly recommended that this model document be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the document.

The investigator has the final responsibility for the final presentation of Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the investigator with the assistance of the sponsor's representative, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to GSK Biologicals.

In addition to the Informed Consent Form at Visit 1 to participate in this study, parents/guardians will be presented with an informed consent form summary and a feedback form as well as a second Informed Consent Form to obtain consent for HIV testing of the subjects. The HIV test will be proposed and ideally performed at visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006).

The parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi, who are interested to continue the participation of their child in the second year follow-up will be presented a supplementary ICF at Visit 6 to obtain their written informed consent.

A supplementary ICF will also be given to the parents/guardians of subjects at Visit 6 (irrespective of their decision to let their child/ward participate in the second year follow-up period) to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed. (Amendment 6: 2 August 2007).

5.2. General study aspects

- Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa. (South Africa-specific Amendment 5: 10 July 2006)
- Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit 1. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Pre-test counselling and informed consent for HIV testing will be performed. A blood sample will be obtained from all subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on collected blood samples will be communicated to the parents/guardians at the subsequent visit/contact. Post-test counselling will be offered to mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive after the initial test and are asymptomatic, a confirmatory HIV test should be performed at the subsequent visit. Results of the HIV test should be recorded in the CRF. Subjects who undergo the initial HIV testing at Visit 4 will have an additional visit so that the study staff can inform parents/guardians of HIV test results and offer post-test counselling. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

  In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [South African National Department of Health Guidelines for the Management of HIV-infected Children 2005] and Standard of Care provided during GSK sponsored trials. (South Africa-specific Amendment 5: 10 July 2006)

  In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi (1st edition October 2003 or later edition)] and Standard of Care provided during GSK sponsored trials. (Amendment 2: 27 October 2005) (Malawi-specific Amendment 3: 22 February 2006)

  The study staff will, where clinically indicated and/or for hospitalised HIV positive children, facilitate access of study subjects to a HIV staging facility and/or ARV treatment centers during the study, but decisions towards treatment will be taken by appropriate staff at these treatment centers. (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

- During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 in South Africa, and from Visit 1 up until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)
- In Malawi, the study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health. (Malawi-specific amendment 4: 15 May 2006)
- In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed (due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed. (South Africa-specific Amendment 5: 10 July 2006)
- National Guidelines for the management of HIV infected children in South Africa recommend HIV testing 6 weeks after breast feeding cessation and the National Guidelines in Malawi for the management of HIV infected children recommends the HIV testing 3 months after breast feeding cessation. This testing will be done through the usual clinic/paediatric outpatient system. The results of repeat test after breast feeding ceases should be recorded in the CRF. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)
- As part of the clinical practice at the study site, mothers together with their infants who are HIV positive will be offered support and facilitated access to ARV treatment centers where they will receive prophylaxis and care. (Amendment 1: 24 August 2005)

- As part of the clinical practice at the study site, infants who have diarrhoea should be offered care and treatment at the study site during the study. (Amendment 1: 24 August 2005)
- Hepatitis B, BCG and OPV vaccinations at birth are allowed according to local EPI schedule and should be documented in the CRF. (Amendment 1: 24 August 2005)
- Routine EPI schedule vaccinations (DTPw-HB/Hib and OPV) should be administered concomitantly with the study vaccine at Visit 1, 2 and 3 following the EPI recommendation (at approximately 6, 10 and 14 weeks of age) and documented in the CRF. (Amendment 1: 24 August 2005).
- BCG at Visit 1 is allowed and should be documented in the CRF. (Amendment 1: 24 August 2005)
- There will be no restrictions on feeding the infants before or after study vaccine administration.
- Parents/guardians of all subjects will receive a Trial Identification Card, which will specify details of the trial, 24-hour telephone number of the study physicians, study coordinator and study staff. Parents/guardians may contact the study physician, study coordinator or study staff in case of any AEs. Parents/guardians will be instructed to attend the local clinic or hospital for after-hours consultation. Physicians and nurses at the local clinic or hospital will be fully informed of the trial and may contact the study physician for further advice. Parents/guardians will be instructed to show the Trial Identification Card to any health care professional they consult.
- GE surveillance:

  Active surveillance for GE (diarrhoea) will be conducted by the study staff during the entire study period (starting at Dose 1 until Visit 6 for subjects in Cohort 1 South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi). Study staff will visit the subject every week to check for the occurrences of any GE during the entire study period. Parents/guardians of study subjects will be instructed to contact the study staff in case of diarrhoea. The study staff will direct the parents/guardians to the nearest hospital/medical facility as necessary. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

  For each GE episode occurring during the study period, a ‘GE diary card’ should be completed daily until end of diarrhoea. Parents/guardians should collect stool samples during the GE episode as described below. Detailed procedures for follow-up of GE episodes will be given in a separate booklet that will be provided to all investigators.

- Collection of stool samples:

  Parents/guardians of all subjects will be instructed to collect stool sample(s) if the subject develops diarrhoea at any time until Visit 6 for subjects in Cohort 1 in South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi (Amendment 6: 2 August 2007). Diarrhoea is defined as passage of three or more looser than normal stools or watery stools within a day. (Amendment 1: 24 August 2005)

Parents/guardians should collect a stool sample as soon as possible after the symptoms begin, and preferably not later than 7 days after the start of diarrhoea. A second stool sample will be collected if the first sample was insufficient. Parents/guardians will be asked to record whether they sought medical attention and whether medication was administered. Two occurrences of GE should be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.

5.2.1. Independent Data Monitoring Committee (IDMC)

An IDMC consisting of clinical experts and a biostatistician has been charged with monitoring the safety aspects of the HRV vaccine clinical development: i.e. each SAE case and each case fatality is reviewed unblinded by treatment group by this committee.

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

(Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

Table 1 List of study procedures for Cohort 1 and 2 enrolled in South Africa and all subjects enrolled in Malawi

Age	**5-10 weeks**						
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**	**VISIT 7**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**1 year of age**	**End of 2nd efficacy follow-up period**
Sampling timepoint	**Pre**			**Post vacc 3**			
Informed consent	•						
Informed consent addendum for HIV testing§	•			•			
Supplementary ICF for using results of HIV testing performed after breast feeding cessation						•	
Supplementary ICF for participation in 2nd efficacy follow-up						•	
Medical history	•						
Medical history for HIV	•						
Check of inclusion criteria	•						
Check of exclusion criteria	•						
Check of elimination criteria		•	•	•		•	•
Check of contraindications	•	•	•				
Randomisation	•						
Physical examination	•	#	#	#		#	#
Pre-vaccination body temperature	•	•	•				
Measure/record height and weight	•			•		•	•
Blood sampling							
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects			
For HIV testing, if and when accepted‡	• (3 ml in South Africa and 1 ml in Malawi)			• (3 ml in South Africa and 1 ml in Malawi)			
Confirmatory HIV testing, if required		• (2 ml in South Africa and 1 ml in Malawi)			• (2 ml in South Africa and 1 ml in Malawi)		
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•	•
Study vaccination (HRV or placebo)	•	•	•				

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Age	**5-10 weeks**						
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**	**VISIT 7**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**1 year of age**	**End of 2nd efficacy follow-up period**
Sampling timepoint	**Pre**			**Post vacc 3**			
Routine EPI vaccination	•	•	•				
Recording of AEs leading to drop-out	•	•	•	•		•	•
Return of completed diary cards by parents/guardians		•	•	•		•	•
Diary card transcription		•	•	•		•	•
Recording concomitant medication/vaccination	•	•	•	•		•**	•**
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•	•
Record results of HIV testing		•	•		•		
Inform subjects of HIV result		•	•		•		
Record results of HIV testing after breast feeding ceases						•	•
Study Conclusion						•	•

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries (See Section 5.5 and Section 5.6.2). (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

†Visit 5 will take place 21-48 days after Visit 4 only in subjects who had an initial HIV test at Visit 4 (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

• is used to indicate a study procedure which requires documentation in the individual CRF. (Amendment 1: 24 August 2005)

* = The blood sample will be collected before administering the dose of vaccine/placebo.

‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

§During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 in South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the cohort in Malawi), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

is used to indicate a study procedure which does not require documentation in the individual CRF. (Amendment 1: 24 August 2005)

•** Only concomitant medication administered for treatment of GE, AE leading to drop-outs and SAEs will be recorded during this period.

Visit 7 is for subjects in Cohort 2 South Africa and the Cohort in Malawi only.

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

Table 2 Intervals between study visits for Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

(Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Interval	Size of interval
1 (Visit 1→Visit 2)	28 to 48 days
2 (Visit 2→Visit 3)	28 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days
4 (Visit 4→Visit 5)	21 to 48 days
Visit 6	343-391 days of age
Visit 7	1 August 2008 - 15 September 2008 (end of RV season) for Cohort 2 South Africa and until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) for the Cohort in Malawi

(Amendment 6: 2 August 2007)

Refer to Annex 3 for list of study procedures and intervals between study visits for cohort 1 enrolled in South Africa. (South Africa-specific Amendment 5: 10 July 2006)

5.5. Detailed description of study visits

(Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Cohort 1 enrolled in South Africa

Refer to Annex 3 for detailed description of study visits for cohort 1 enrolled in South Africa.

Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.
- Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians give consent.

When materials are provided by GSK Biologicals or designated laboratory, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting

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

- Record results of the HIV test at the subsequent visit in the CRF.
- Only in subjects who test HIV positive at the initial test and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test.

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Record results of the confirmatory HIV test at the subsequent visit/contact in the CRF.
- Communicate HIV test result of the confirmatory HIV test to parents/guardians at the subsequent visit/contact and post-test counselling.

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- Written informed consent from the parent/guardian of the subject.
- Proposal for HIV testing to parents/guardians. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Record medical history with regards to HIV exposure in the CRF. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Medical history taking.
- Check of inclusion/exclusion criteria.
- Check contraindications to vaccination.
- HBV, BCG and OPV doses administered at birth should be recorded in the CRF. Record any prior/concomitant vaccinations administered in the CRF.
- Randomisation (or subject) number attribution.
- Physical examination and recording of height and weight.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Collection of pre-vaccination blood sample for serology from a subset of 570 subjects: (Amendment 2: 27 October 2005)

In South Africa, a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.

In Malawi, a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Vaccination:

Oral administration of Dose 1 of the HRV vaccine or its placebo.

Administration of Dose 1 of the routine EPI vaccine (DTPw-HB/Hib and OPV) in all groups. (Amendment 1: 24 August 2005)

All vaccines should be administered according to the guidelines set out in Section 6.2. All administered vaccines should be recorded in CRF.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 2. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any signs or symptoms and that they perceive as serious.
- Parents/guardians will be instructed to attend the local hospital, close to the site of the clinics for after-hours consultation.

Visit 2, Month 1, Dose 2 (28-48 days after Visit 1)
(Amendment 2: 27 October 2005)

- Physical examination.
- Check of elimination criteria.
- Check contraindications to vaccination.
- Recording of SAEs that may have occurred since the previous visit.
- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Return any stool samples.
- If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling and collection of blood samples for confirmatory HIV test if required. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Record AEs leading to drop-out in the CRF.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Vaccination:

Oral administration of Dose 2 of the HRV vaccine or its placebo.

Administration of Dose 2 of the routine EPI vaccine (DTPw-HB/Hib and OPV) in all groups. (Amendment 1: 24 August 2005)

All vaccines should be administered according to the guidelines set out in Section 6.2. All administered vaccines should be recorded in CRF.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 3. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in

Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.

- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.
- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.

Visit 3, Month 2, Dose 3 (28-48 days after Visit 2)
(Amendment 2: 27 October 2005)

- Physical examination.
- Check of elimination criteria.
- Check contraindications to vaccination.
- Recording of SAEs that may have occurred since the previous visit.
- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Return any stool samples.
- If confirmatory HIV test done at the preceding visit, communicate the results of the HIV to parents/guardians, record results of HIV test in the CRF and post-test counselling. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Record AEs leading to drop-out in the CRF.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Vaccination:

Oral administration of Dose 3 of the HRV vaccine or its placebo.

Administration of Dose 3 of the routine EPI vaccine (DTPw-HB/Hib and OPV) in all groups. (Amendment 1: 24 August 2005)

All vaccines should be administered according to the guidelines set out in Section 6.2. All administered vaccines should be recorded in CRF.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.

- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 4. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.
- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- Proposal for HIV testing to parents/guardians, if HIV testing not done previously. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)
- Physical examination.
- Check of elimination criteria.
- Recording of height and weight.
- Recording of SAEs that may have occurred since the previous visit.
- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Record AEs leading to drop-out in the CRF.
- Return any stool samples.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Collection of a blood sample for serology from all subjects: (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)

In South Africa, a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.

In Malawi, a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.

- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 6. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit. (Amendment 1: 24 August 2005)
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.
- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.
- Parents/guardians will be reminded to attend their usual clinic for recommended routine vaccinations (Measles and DTPw/HBV/Hib booster).

Visit 5, Month 4, Follow-up (21- 48 days after Visit 4) Only for subjects who had initial HIV test at Visit 4 (Amendment 1: 24 August 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

- If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling, collection of blood samples for confirmatory HIV test if required and planning for a contact to inform the parents/guardians about the confirmatory HIV test result in 2 weeks. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Visit 6, Follow-up (343-391 days of age) (Amendment 1: 24 August 2005)

(Amendment 6: 2 August 2007)

- Physical examination.
- Recording of height and weight.
- Check of elimination criteria.
- Recording of SAEs that may have occurred since Visit 4.
- Record any concomitant medications administered for the treatment of GE, SAEs and AEs leading to drop-outs in the CRF.
- The parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi, who are interested to continue the participation of their child in the second year follow-up will be presented a supplementary ICF to obtain their written informed consent.

- A supplementary ICF will be presented to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed.
- Record results in the CRF if the HIV test was repeated after breast feeding cessation. (Amendment 1: 24 August 2005)
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Return any stool samples.
- Record AEs leading to drop-out in the CRF.
- A 'GE diary card' will be provided to parents/guardians of all subjects who provide consent to continue participation during the second efficacy follow-up period, and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 7. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the subject manifests any of these signs or symptoms and that they perceive as serious.
- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.

(Amendment 6: 2 August 2007)

Visit 7, Follow-up (end of RV season 2008 i.e. between 1 August 2008 and 15 September 2008 for subjects in Cohort 2 South Africa and until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009 for all subjects in Malawi) Visit 7 is for subjects in Cohort 2 South Africa and Cohort in Malawi only. (Amendment 6: 2 August 2007)

- Physical examination.
- Recording of height and weight.
- Check of elimination criteria.
- Record any concomitant medications administered for the treatment of GE, SAEs and AEs leading to drop-outs in the CRF.
- Recording of SAEs that may have occurred since Visit 6.
- Record results of HIV testing after breast feeding cessation in the CRF if consent to use the results was obtained from the parents/guardiand and if the HIV test was perfomed since the previous visit.

- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Return any stool samples.
- Record AEs leading to drop-out in the CRF.
- Study conclusion.

(Amendment 6: 2 August 2007)

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.

Back-ups of stool samples will be maintained (see Appendix D) and should be used only for additional shipments in case mailed samples are lost. (Amendment 2: 27 October 2005)

5.6.2. Laboratory read outs

The GSK Biologicals' laboratory at Rixensart has established Quality Control Procedures and an established Quality System. Both are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department to document the competency of the facility to perform the required tests and support the reliability of the results. Methods and equipment are validated, where required.

GE Stool analysis

All stool samples collected during diarrhoea episodes from Visit 1 to Visit 7 will be processed at the study site or designated laboratory and shipped frozen to GSK Biologicals, Belgium. The stool samples will be analyzed at GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using ELISA to detect RV. If a stool sample tests positive for RV, the sample will be tested by Polymerase Chain Reaction (PCR) to determine the serotype. If any G1 RV is detected in the stool specimens, vaccine virus may be differentiated from the wild type serotype by sequence analysis or an equivalent approach. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

Serum analysis

Blood samples collected from a subset of 570 subjects at Visit 1 and from all subjects at Visit 4 will be centrifuged and the separated serum should be stored at –20°C until shipped to GSK Biologicals, Belgium for analysis. (Amendment 1: 24 August 2005)

Anti-rotavirus IgA antibody concentrations at Visit 1 (in a subset) and Visit 4 (in all subjects) will be measured by ELISA. The assay cut-off is 20 U/ml.

HIV assay

(Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

HIV testing will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at the initial test and are asymptomatic, a confirmatory HIV test should be performed at the subsequent visit.

During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing and the concerned informed consent will be will be proposed at the site, in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (Amendment 6: 2 August 2007)

HIV tests will be performed locally at designated laboratories accredited for HIV testing and using approved test kits (see last updated version of laboratory workbook for details of blood sample collection, transportation and testing).

South Africa

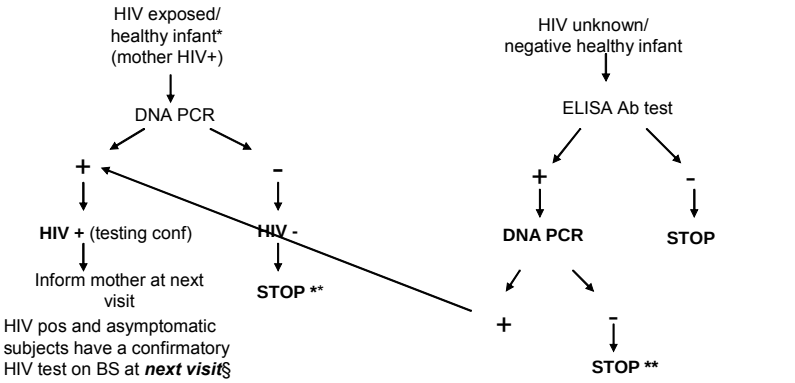
HIV testing will be done according to the algorithm presented in Figure 1 (see below) based on the guidelines HIV testing guidelines in children from the Department of Health, South Africa [South African National Department of Health Guidelines for the Management of HIV-infected Children 2005] as outlined in Annex 2. (South Africa-specific Amendment 5: 10 July 2006)

National Guidelines in South Africa recommend HIV testing 6 weeks after breast feeding cessation. This testing will be done through the usual clinic/paediatric outpatient system. The results of the repeat test after breast feeding ceases should be recorded in the CRF. (South Africa-specific Amendment 5: 10 July 2006)

In case of discrepancy between HIV test results at initial and confirmatory tests (HIV positive at initial test, negative at confirmatory test), the HIV test should be repeated on the confirmatory test blood sample If the discrepancy remains, the child should be sent to an ARV roll out center for HIV repeat test on a new blood sample according to National Guidelines in South Africa. (South Africa-specific Amendment 5: 10 July 2006)

Figure 1 Algorithm for HIV testing in South Africa

(Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (South Africa-specific Amendment 5: 10 July 2006)



* If infant has signs of HIV infection or has to be hospitalized (WHO interim stages III and IV) and any HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible
** In South Africa: If breast-feeding : repeat test 6 weeks after breast-feeding cessation
§ documented study contact for subjects with confirmatory HIV test

Note: DNA testing using PCR as specified in the Figure 1 is applicable to subjects only up to 18 months of age, whose mothers tested positive for HIV or for whom their mother's status was not known but the ELISA was reactive. ELISA tests would be performed on subjects after 18 months of age. As per the South African Guidelines no DNA PCRs will be performed for subjects after 18 months of age (Amendment 6: 2 August 2007).

Malawi

For all subjects whose parents gave consent for HIV testing, HIV status will be determined by employing 2 commercially available rapid HIV antibody tests, currently in use by the Malawi's HIV-testing program (Determine and Unigold). When any of the two rapid HIV antibody test results are positive, PCR testing will be done. Subjects who test HIV positive at the initial test and are asymptomatic will undergo PCR testing at the time of the confirmatory test. (Malawi-specific Amendment 3: 22 February 2006) (Malawi-specific amendment 4: 15 May 2006)

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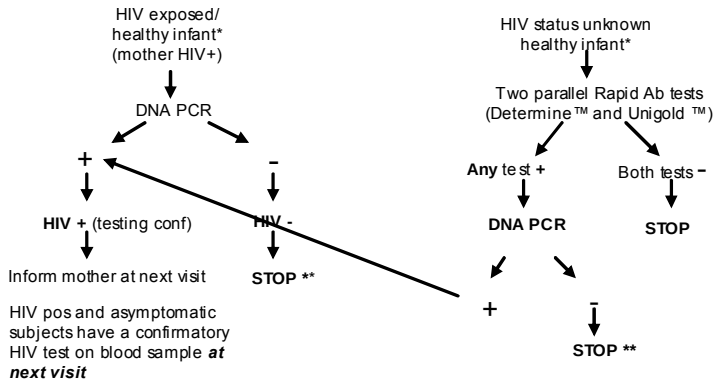
Figure 2 Algorithm for HIV testing in Malawi

(Malawi-specific Amendment 3: 22 February 2006) (Malawi-specific amendment 4: 15 May 2006)



* If infant has signs of HIV infection (WHO interim stages III or IV) or has to be hospitalised, and any HIV testing has not yet been performed, HIV testing and the concerned Informed Consent will be proposed to the mothers

** If breast-feeding : repeat test at 3 months after breast-feeding cessation.

Table 3 Read-outs

(Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific Amendment 3: 22 February 2006) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times from Visit 1 until Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi (Amendment 6: 2 August 2007))			RV antigen	All	None
Serum analysis					
Timing	**Month**	**Visit no**			
Pre	Day 0	1	IgA anti-HRV	Subset of 570 subjects	None
Post-vacc 3	Month 3	4	IgA anti-HRV	All	None
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
HIV test			Serum HIV antibody test (ELISA)	Subjects not exposed to HIV or HIV status unknown	None
			Whole blood DNA PCR	- Subjects not exposed to HIV and positive for HIV antibody - Subjects exposed to HIV	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at the initial HIV test and asymptomatic	None
Malawi					
HIV test			rapid HIV antibody tests	All	None
			Whole blood DNA PCR	Subjects positive by any of the two rapid HIV antibody tests or in case of discrepancy	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at the initial HIV test and asymptomatic	None

Any additional testing on biological samples to further evaluate the immunogenicity of the HRV vaccine (such as neutralisation assay) will be performed if deemed necessary by GSK Biologicals if any findings in the present study necessitate further investigation of the vaccine. (Amendment 1: 24 August 2005)

In South Africa, based on the result of the HIV assay, access to further testing, treatment or counselling will be available to subjects in South Africa as per the national guidelines in South Africa [South African National Department of Health Guidelines for the Management of HIV-infected Children 2005] (also refer to Section 5.2). (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and

Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi (1st edition October 2003 or later edition)] (also refer to Section 5.2). (Amendment 2: 27 October 2005) (Malawi-specific Amendment 3: 22 February 2006)

5.6.3. Endpoints for suboptimal response

Not applicable.

6. INVESTIGATIONAL PRODUCTS AND ADMINISTRATION

6.1. Study vaccines

The candidate vaccine 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.

Vaccine	Formulation	Presentation	Volume
GSK Biologicals' HRV vaccine	RIX4414 HRV strain $10^{6.5}$ CCID50 Dulbecco's Modified Eagle Medium (DMEM) 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised product in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' Placebo for HRV vaccine	DMEM 3.7 mg Sucrose 9 mg Dextran 18 mg Sorbitol 13.5 mg Amino acids 9 mg	Lyophilised product in monodose glass vial. Diluent (calcium carbonate buffer) supplied separately.	Not applicable
GSK Biologicals' calcium carbonate buffer	Calcium carbonate 80 mg Xanthane 0.25 % in Water for Injection 1.3 ml	Liquid buffer in pre-filled syringe.	1.3 ml

Several lots of the HRV vaccine and placebo may be used.

Refer to Appendix G for details of vaccine supplies.

6.2. Dosage and administration

HRV vaccine or placebo

To prepare GSK Biologicals' HRV vaccine or its placebo for administration, the entire content of the supplied calcium carbonate buffer should be injected into the vial of the lyophilised product (vaccine or placebo). The vial should be shaken well to resuspend the vaccine. The entire volume of the resuspended product should be withdrawn into the same syringe. In case a needle is used, it should be discarded. The resuspended product should then be administered promptly as a single oral dose.

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Should the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered at that visit. The subject may continue to participate in the study and will not be excluded from the planned analyses. (South Africa-specific Amendment 5: 10 July 2006)

The study vaccination regimen is summarised in Table 4.

Table 4 Dosage and Administration

Group	Visit 1	Visit 2	Visit 3
HRV 3-dose	HRV	HRV	HRV
HRV 2-dose	Placebo	HRV	HRV
Placebo	Placebo	Placebo	Placebo

Study vaccines and all routine vaccines administered should be documented in the CRF. (Amendment 1: 24 August 2005)

6.3. 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°C to +8°C/ 36°F to 46°F).

The storage temperature of vaccines will be monitored and recorded daily during working days, preferably at the same time of the day (e.g. at the beginning of the day).

At a minimum, a calibrated/validated min/max thermometer will be placed close to the vaccines and will be used to monitor and record the daily temperature (actual, min and max temperatures will be logged). Additionally, a continuous temperature recording system (e.g. 90-day Cox Recorder) will be used as a back up device and it will be opened in case of any temperature deviation (temperature outside the defined range, i.e. +2°C to +8°C/ 36°F to 46°F) during weekends or holidays.

Alternatively, the temperature monitoring system of the storage facility can be used (as a replacement of the GSK continuous temperature recording system), if:

- proper functioning was demonstrated during the monitor's site evaluation,
- if the system continues to work in case of a power failure, and
- if the system is maintained regularly (e.g. once/year) as documented in the site files.

It is also permitted to monitor the storage temperature using a validated temperature continuous recording device, provided it can read the daily actual and min/max temperatures, and that it keeps working after the alarm is activated.

It is also required to place a validated freezing point indicator (e.g. Freeze Tag) close to the vaccines as a back-up device.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2°C 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 center to study sites or between sites are described in Appendix G.

6.4. Treatment allocation and randomisation

Target enrolment will be 4,800 subjects (1,600 subjects in each group) (Amendment 6: 2 August 2007).

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 (1:1:1 ratio) will be used to ensure that balance between treatments is maintained: throughout the study, a single treatment number will uniquely identify the vaccine doses to be administered to the same subject.

To allow GSK Biologicals to take advantages of greater rates of recruitment than anticipated at individual centres in this multicenter study, and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared. (South Africa-specific Amendment 5: 10 July 2006)

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

6.4.2. Randomisation of subjects

At Visit 1, subjects will be administered the vaccine dose with the lowest treatment number still available at the study site.

The actual treatment number used for first vaccination of the subject must be recorded by the investigator in the CRF (Rando/Treatment Allocation Section). (Amendment 1: 24 August 2005)

6.4.3. Subset

The subset of 570 subjects (190 subjects per group) from selected sites will provide a blood sample at Visit 1 (Amendment 1: 24 August 2005). No subjects from cohort 2 in

South Africa will be part of the subset providing blood samples at Visit 1. (South Africa-specific Amendment 5: 10 July 2006)

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 administered treatment (HRV vaccine or placebo). Blinding will be maintained for the whole study period (see Section 10.7 for details on how the individual blinding will be maintained despite statistical analyses before all study data are collected/processed). This will allow unbiased evaluation of the study vaccine. (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007).

A set of individual codes will be held at the GSK Biologicals' Central Safety Office. The code will be broken by the Clinical Safety physician (Study Contact for Emergency Code Break in Sponsor Information page) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s). (South Africa-specific Amendment 5: 10 July 2006)

GSK Biologicals' policy (incorporating ICHE2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any 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).

The IDMC will be informed of each SAE on an ongoing basis. The IDMC will have access to the individual codes and may at its discretion decode the SAEs to identify the product administered to any subject and evaluate whether enrolment in the study should be halted.

6.6. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix G for details of supplies).

In addition to the vaccine doses provided for the planned number of subjects, 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 CRF and on the vaccine accountability form. (Amendment 1: 24 August 2005)

Individual sealed envelopes with coded letters will be given to investigators in order to 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

(Amendment 1: 24 August 2005)

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 at Visit 1 and ending at 31 days post last vaccine dose are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or placebo are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment. Refer to Sections 4.3 and 4.4.

All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF with trade name, route of administration and date(s) of administration. Refer to Sections 4.3 and 4.4.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C, oral temperature < 37.5°C or axillary temperature < 37.5°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the CRF 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 a SAE and AE* within the follow-up period for adverse events must be recorded in the CRF 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 (from Visit 1 to Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi) must be recorded in the CRF. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

Any ARV therapy given throughout the study (from Visit 1 to Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi) must be recorded in the CRF. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

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 AE leading to drop-out (AE*) or 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 leading to drop-out 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

This section applies to AEs leading to subject withdrawal/drop-out.

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

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.

Examples of an AE DO NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Example of events to be recorded in the medical history section of the CRF (Amendment 1: 24 August 2005):

- 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).

8.2. Definition of a serious adverse event

A 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.

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

e. 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.

f. is a congenital anomaly/birth defect in the offspring of a study subject.

g. 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 jeopardise 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.

h. Family permission for Physical Autopsy should be requested in all cases of fatalities, and where this can not be obtained a verbal autopsy should be conducted by the investigator's research staff.

8.2.1. Disease-related events or outcomes not qualifying as serious adverse events

Not applicable.

8.3. Lack of efficacy

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the AE or SAE definition (including clarifications).

8.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, vital signs, etc.) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1 or SAE, as defined in Section 8.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs.

The investigator should liaise with treating physician (if different from investigator) in all cases where study participants are hospitalised with SAE.

During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

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 leading to subject withdrawal or drop-out and serious adverse events

All AEs leading to subject withdrawal/drop-out during the period starting at Visit 1 and ending at Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi must be recorded in the subject's CRF. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

The standard time period for collecting and recording SAEs will begin at Visit 1 and will end at the last study visit foreseen for each subject. See Section 8.7 for instructions for reporting and recording SAEs.

Additionally, in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. procedures, invasive tests, a change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

The investigator will inquire about the occurrence of SAEs at every visit/contact during the study.

When an AE leading to subject withdrawal or drop-out (AE*) or 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 AE*/SAE on the CRF or SAE Report Form as applicable. (Amendment 1: 24 August 2005) It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals in lieu of the appropriate completed AE*/SAE pages. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all

subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE*/SAE and not the individual signs/symptoms.

8.6. Evaluating AE leading to subject withdrawal or drop-out (AE*) and serious adverse events

8.6.1. Assessment of intensity

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for AEs leading to drop-out and SAEs reported from Visit 1 to Visit 6 for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi. The assessment will be based on the investigator's clinical judgement. (Amendment 6: 2 August 2007)

The intensity of each AE and SAE recorded in the CRF or SAE Report Form, as applicable, should be assigned to one of the following categories (Amendment 1: 24 August 2005):

1 (mild)	=	AE*/SAE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	AE*/SAE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	AE*/SAE 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. In adults/ adolescents, such an AE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy.)

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 transmission of the SAE Report Form to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE Report Form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AE*/SAEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE*/SAEs could be causally related to vaccination rather than to the individual vaccines.

Causality of all AE*/SAEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE*/SAEs may have been caused by the investigational product?

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

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 SAEs), it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each SAE.

Other possible contributors include:

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

8.7. Follow-up of serious adverse events/ AE leading to subject withdrawal or drop-out (AE*) and assessment of outcome

After the initial SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous 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;

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.

During the entire study period (from Visit 1 up until Visit 6 for subjects in Cohort 1 South Africa and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or in the case of hospitalisation, at hospital admission if possible. For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms. HIV testing performed at hospital admission should be recorded in the CRF. (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006) (Amendment 6: 2 August 2007)

In addition, the Study Staff will follow the following steps:

- Request permission for a post-mortem for the analysis of the cause of death.
- Request permission for a verbal autopsy, where a post-mortem is refused by the family. The standard WHO Verbal Autopsy questionnaire will be employed. This is utilised on ongoing rotavirus vaccine trials in South Africa and the study staff is trained in its use.
- Study Staff will assess clinically and, where possible, with existing and appropriate laboratory analyses the likely cause of death.

The deaths will be reported to the IDMC. The unblinding of the randomisation codes will be left to their discretion.

New or updated information will be recorded on the originally completed SAE Report Form, with all changes signed and dated by the investigator. The updated SAE report form should be resent to GSK Biologicals within 24 hours of receipt of the follow-up information as outlined in Section 8.8.1.

Outcome of any non serious AE leading to subject withdrawal or drop out or any SAE reported during the entire study will be assessed as:

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

8.8. Prompt reporting of serious adverse events to GSK Biologicals

8.8.1. Time frames for submitting serious adverse event reports to GSK Biologicals

SAEs will be reported promptly to GSK once the investigator determines that the event meets the protocol definition of an SAE. The investigator or designate will fax the SAE reports to GSK Biologicals' Study Contact for SAE Reporting **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS**. Additional or follow-up information relating to the initial SAE report is also to be reported to the GSK Biologicals' Study Contact for SAE Reporting within 24 hours of receipt of such information.

8.8.2. Completion and transmission of serious adverse event reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours as outlined in Section 8.8.1. The SAE Report Form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received and forwarded to GSK **WITHIN 24 HOURS** as outlined in Section 8.8.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.6.2.

Facsimile (Fax) transmission of the SAE Report Form is the preferred method to transmit this information to the Study Contact for Reporting SAEs. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE Report Form within 24 hours as outlined in Section 8.8.1.

In the event of a death determined by the investigator to be related to vaccination, sending of the fax must be accompanied by telephone call to the Study Contact for Reporting SAEs.

The Standard Verbal Autopsy Questionnaire (see Appendix H) [World Health Organization, 1999] 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 a written autopsy is performed or not. The Standard Verbal Autopsy Questionnaire does not replace the written autopsy report.

The Study Contacts per country (where available) are provided as a separate protocol attachment (refer to Attachment 1); in the case where the Study Contact is not available, you must contact the back-up Study Contact (see below). (Amendment 2: 27 October 2005)

Study Contact for Reporting SAEs
Refer to the Sponsor Information Sheet
Back-up Study Contact for Reporting SAEs Refer to the Sponsor Information Sheet
GSK Biologicals Clinical Safety Physician Tel: [redacted] Fax: [redacted] [redacted]
Mobile phone for 7/7 day availability: [redacted] (Head Safety Evaluation and Risk Management Paediatrics) Back-up mobile phone contact: [redacted]
24/24 hour and 7/7 day availability

(Amendment 6: 2 August 2007)

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 Good Clinical Practice (GCP) requirements, regarding the product under investigation.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals will file it with the Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.10. Post study serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE detection period defined in Section 8.5. Investigators are not obligated to actively seek SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.11. Assessment of intensity of GE episodes

The completion of the diary card for each GE episode will allow the assessment of the intensity by using a 20-point scale [Ruuska, 1990]. In this system, points will be assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, presence of dehydration or hospitalisation for each episode of GE as shown below:

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∗ The highest temperature recorded during the episode will be scored.
** Dehydration will be assessed clinically based on World Health Organisation criteria.

A score ≥11 is prospectively defined as severe. A score 7 - 10 is prospectively defined as moderate. A score <7 is prospectively defined as mild.

Information on behavioural symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems. (Amendment 1: 24 August 2005)

8.12. Treatment of adverse events

Treatment of any adverse event ***leading to drop-outs and SAEs*** is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE* and ***SAEs*** should be recorded in the subject's CRF. Refer to Section 6.9. (Amendment 1: 24 August 2005)

In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [South African National Department of Health Guidelines for the Management of HIV-infected Children 2005] and Standard of Care provided during GSK sponsored trials. (South Africa-specific Amendment 5: 10 July 2006). In Malawi, procedures to be followed for ARV therapy will be in compliance

with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi (1st edition October 2003 or later edition)] and Standard of Care provided during GSK sponsored trials. The study staff will, where clinically indicated and/or for hospitalised HIV positive children, facilitate access of study subjects to a HIV staging facility and/or ARV treatment centers during the study, but decisions towards treatment will be taken by appropriate staff at these treatment centers. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific Amendment 3: 22 February 2006) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006)

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who returns for the concluding visit 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 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 CRF (Amendment 1: 24 August 2005). 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 CRF. (Amendment 1: 24 August 2005) 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 severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains in pooled HRV groups versus the placebo group during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

10.2. Secondary endpoints

Efficacy

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 6. (Amendment 1: 24 August 2005)
- In South Africa, occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

For subjects in Cohort 2 South Africa and the cohort in Malawi:

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

(Amendment 6: 2 August 2007)

Safety

- For all subjects, occurrence of AEs/SAEs leading to drop-out throughout the entire study period.
- For all subjects, occurrence of SAEs throughout the entire study period.

Immunogenicity

- In a subset of subjects, seroconversion rate and Geometric Mean concentration (GMC) to anti-rotavirus IgA antibody at Visit 4.
- In all subjects, seropositivity rate and GMC to anti-rotavirus IgA antibody at Visit 4.

10.3. Estimated sample size

(Amendment 1: 24 August 2005)

A total of 4,800 subjects (1,600 subjects in each group) will be enrolled. Allowing for approximately 15% of subjects who may not be evaluable for analyses of the primary objective, 3,960 evaluable subjects (1,320 subjects in each group) are expected to be evaluable for the analysis of the primary objective.

Considering a 1:1:1 randomisation ratio and various incidence rates expected in the study, Table 5 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy.

Assuming a 2% incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of 3,960 evaluable subjects has 84% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).

Table 5 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,320 evaluable subjects, N HRV pooled groups = 2,640 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6		
	60%*	70%	80%
1%	50%	69%	86%
1.5%	71%	87%	97%
2%*	84%	95%	99%
3 %	95%	99%	99%

*Anticipated incidence rate

Table 6 presents the power to detect a statistically significant difference between each HRV group and placebo group for a range of vaccine efficacy.

Table 6 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,320 evaluable subjects, N HRV group = 1,320 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6		
	60%	70%	80%
1%	38%	55%	73%
1.5%	57%	76%	90%
2%*	71%	88%	97%
3 %	89%	97%	99%

*Anticipated incidence rate

The study is not powered to compare the efficacy of the 2-dose and the 3-dose schedules.

Estimation of power for the second efficacy period

With respect to the year 2 efficacy follow-up, Table 7 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy. If the VE is truly 60% and assuming a 2% incidence of severe RV GE in the placebo group, a sample size of 2325 evaluable subjects has 59% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95% CI on vaccine efficacy > 0%).

Table 7 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 775 evaluable subjects, N HRV pooled groups = 1550 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from Visit 6 up to Visit 7		
	60%*	70%	80%
1%	29%	43%	60%
2%*	59%	78%	92%
3 %	79%	93%	99%

*Anticipated incidence rate

(Amendment 6: 2 August 2007)

10.4. Study cohorts to be evaluated

Total vaccinated cohort

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

- a safety analysis based on the total vaccinated cohort will include all vaccinated subjects.
- an immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects for whom immunogenicity data are available.
- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects. (Amendment 6: 2 August 2007)

According-to-protocol (ATP) safety cohort

The ATP safety cohort will include all vaccinated subjects:

- who have received at least one dose 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.
- who have not received a replacement vial, except if the appropriate vaccine was administered in “double-blind replacement”. (Amendment 6: 2 August 2007)

ATP efficacy cohort

The ATP efficacy cohort will include all subjects from ATP safety cohort:

- who received their full study vaccination course.
- who have entered into the efficacy surveillance period:
  - have follow-up beyond 2 weeks after the last dose of the study vaccination course for analysis of the first and combined efficacy follow-up periods.
  - have follow-up beyond the end of the first efficacy follow-up period for analysis of the second efficacy follow-up period.

(Amendment 6: 2 August 2007)

- who have no RV other than vaccine strain in diarrhoeal stool samples collected between the day of Dose 1 is administered and 2 weeks after the last dose of the study vaccination course.

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 reporting and analysis plan defined age-interval),
- who comply with vaccination schedule for HRV vaccine or placebo (outside reporting and analysis plan defined age-interval),
- who comply with blood sampling schedule (outside reporting and analysis plan defined age-interval),
- for whom immunogenicity data are available, at post sampling timepoint.
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 4.
- who have no concomitant infection unrelated to the vaccine which may influence the immune response.

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 safety cohort 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 with post-vaccination immunological results are excluded from the ATP immunogenicity cohort. In such a case, the total vaccinated cohort analyses evaluate whether exclusion from the ATP cohort have biased the results.

10.5. Derived and transformed data

Efficacy

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

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 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 antibodies (i.e. concentration greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- The GMC calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

Safety

For the analysis of SAE/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject, missing or non-evaluable HIV measurements will not be replaced. Therefore, a safety analysis based on the HIV seropositivity status will exclude subjects with missing or non-evaluable HIV measurements.

10.6. Final analyses

Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. (Amendment 1: 24 August 2005). A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed after subjects have completed Visit 7, and will be presented in an annex report.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 6. However, access to the individual treatment decode will be provided to the investigators only after the final analyses of the second efficacy follow-up has been performed.

(Amendment 6: 2 August 2007)

10.6.1. Analysis of demographics/baseline characteristics

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 will be calculated per group. The racial and gender composition will be presented.

HIV status at Visit 1 and Visit 4 will be presented. (Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo will be calculated per group.

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

The percentages of subjects who received concomitant and intercurrent vaccinations will be tabulated by group.

10.6.2. Analysis of efficacy

Vaccine efficacy will be calculated by HRV group and for pooled HRV groups, with their 95% CI (see Appendix I for mathematical detail) against:

- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- Severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)
- In South Africa, severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)
- Severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6. (Amendment 1: 24 August 2005)

In addition, vaccine efficacy will be calculated, with their 95% CI, against

- severe RV GE caused by the circulating wild-type RV strains, hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical

facility for RV GE, severe RV GE (G1 and non-G1) for the second and combined efficacy periods and for pooled HRV groups.

- severe RV GE caused by the circulating wild-type RV strains after 3 doses of HRV vaccine versus 2 doses of HRV vaccine for the combined efficacy period.

(Amendment 6: 2 August 2007)

The primary objective will be reached if the lower limit of the 95% CI on vaccine efficacy for pooled HRV groups against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 is >0%. (Amendment 1: 24 August 2005)

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE requiring hospitalisation, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, time to events analysis, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system). (Amendment 1: 24 August 2005)

10.6.3. Analysis of safety

The percentage of subjects with SAEs reported during the study period will be tabulated by group according to Medical Dictionary for Regulatory Activities (MedDRA) classification, with its exact 95% CI.

The percentage of subjects with AEs/SAEs leading to subject drop-out will be tabulated by group according to MedDRA classification, with its exact 95% CI.

Exploratory safety analyses will be performed according to the HIV seropositivity status. (Amendment 1: 24 August 2005)

The height and weight increase from Visit 1 to Visits 4, 6 and *7* will be summarised by group. (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)

10.6.4. Analysis of immunogenicity

For each treatment group, at each time point that a given antigen is measured,

- Seropositivity/seroconversion rates and their exact 95% CI will be tabulated.
- GMCs and their 95% CI will be calculated.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 4 will be displayed using reverse cumulative curves.

The asymptotic standardised 95% CI for difference in the percentage of subjects who were seropositive for anti-rotavirus IgA antibody concentrations at Visit 4 between each HRV group and placebo group, and between pooled HRV groups and placebo group will be computed.

10.7. Planned interim analysis

An interim analysis on vaccine efficacy against any RV GE and severe RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be descriptive and will not be used to conclude on vaccine efficacy.The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. The interim analysis will be based on the total vaccinated cohort for the subset of subjects with efficacy follow-up 2 weeks beyond study dose 3. The estimated VE against any wild-type RV GE and severe wild-type RV GE will be provided for the pooled HRV groups versus the placebo group. Distribution of RV GE by serotype will also be available although this will not be provided by group.The interim analysis will be dissemintated within GSK and shared with the Rotavirus Vaccine Program (RVP) organization and the investigators.

Table 8 indicates the level of accuracy that can be expected for the interim evaluation of efficacy against severe RV GE.

Table 8 Power at interim analysis to get an exact confidence interval for the vaccine efficacy above 0% for a true VE of 60% and 70%, and for different total number of severe RV GE episodes reported (ratio 2:1 (pooled HRV groups:placebo), alpha=0.1%, PASS 2005)

Total number of severe RV GE episodes reported in the three groups	Power	
	Vaccine efficacy of 60%	Vaccine efficacy of 70%
80	81%	98%
70	71%	96%
65	65%	94%
60	58%	90%
40	34%	70%
30	25%	54%
20	14%	32%
10	2%	6%

Since the interim analysis will be descriptive and will not be used to conclude on vaccine efficacy, no adjustment on the alpha will be applied for the final analyses of efficacy.

(Amendment 6: 2 August 2007)

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.

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Appendix A World Medical Association Declaration of Helsinki

(Administrative change 1: 22 September 2005)

Recommendations guiding physicians
in biomedical research involving human subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. 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."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognised. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

I BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate 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.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical 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 the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable

benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorised representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

II ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (See footnote)
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. (See footnote)
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the

absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004. (South Africa-specific Amendment 5: 10 July 2006)

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 authorised 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 Practices" (GCP) and all applicable regulatory requirements.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- To permit drug regulatory agencies and GSK audits.
- II. Protocol Amendments and Administrative changes
- No changes to the study protocol will be allowed unless discussed in detail with the GSK Biologicals' Clinical Development Manager/Medical Monitor and filed as an amendment/administrative change to this protocol.
- Any amendment/administrative change to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation, except where permitted by all applicable regulatory requirements; administrative changes and amendments not submitted for approval are submitted to IRBs/IECs for information only.Submission of protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements. For some countries, 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

GSK Biologicals reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. Reasons for suspension or early termination will be documented in the study file at GSK Biologicals.

If GSK Biologicals determines that suspension or early termination is needed, GSK Biologicals will discuss this with the Investigator (including the reasons for taking such action). When feasible, GSK Biologicals will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK Biologicals will promptly inform, via written communication, all investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study. Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and/or institutions and GSK.

IV. Case Report Form Instructions

(Amendment 1: 24 August 2005)

Prior to screening the first potential participant, the investigator will provide the Site Monitor with a list (Site Staff Signature Sheet) showing the name and title, signature and initials of all site staff who have a critical effect on the conduct of the study and to whom the investigator has delegated significant study related duties such as entering data on the CRFs or changing entries on CRFs. If the authorised individuals should change during the study, the investigator is to inform GSK Biologicals GSK Biologicals' representative of the specific change(s).

CRFs (and subject diary cards, if applicable), will be supplied by GSK Biologicals for recording all data. It is the responsibility of the investigator or co-investigator to ensure that study data are legible, accurate, adequately recorded and, when entered on paper copy, completely filled in with a black ink fountain or ballpoint pen.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled and dated (and justified, whenever possible), where necessary, by the authorised individual making the change. The original entry must not be obliterated, overwritten or erased when a correction is made.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the investigator (or designated staff as documented in the Site Staff Signature Sheet) as soon as possible after the last data becoming available. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed promptly after the last data becoming available. This also applies to forms for potential study participants who were screened but not randomised to a study group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed, the investigator or medically qualified sub-investigator to whom this task has been delegated will sign the study conclusion pages of the CRF to confirm that they have reviewed the data and that the data are complete and accurate. In all cases the investigator remains accountable for the study data collected.

An original (top copy) CRF or log sheets must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs are reviewed by a GSK Biologicals' professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors with documentation and approval by the investigator or appropriately qualified designee as documented on the Site Staff Signature Sheet. In all cases, the investigator remains accountable for the study data. Wherever possible the investigator should assist in the clarification or correction of errors detected after study finalisation promptly after being brought to the attention of the investigator (preferably within 5 working days).

Any questions or comments related to the CRF should be directed to the assigned Site Monitor.

V. Monitoring by GSK Biologicals

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place early in the study, during the study at appropriate intervals and after the last subject has completed the study. It is anticipated that monitoring visits will occur at a frequency defined and communicated to the investigator before study start.

These visits are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical practice (GCP) and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study. Direct access to all study-related site and source data/ documents is mandatory for the purpose of monitoring review. The monitor will perform a CRF review and a Source Document verification (verifying CRF entries by comparing them with the source data/documents that will be made available by the investigator for this purpose: any data item for which the CRF will serve as the source must be identified, agreed and documented. Data to be recorded directly into the CRF pages/RDE screens will be specified in writing preferably in the source documentation agreement form that is contained in both the monitor's and

investigator's study file. For RDE, the monitor will mark completed and approved screens at each visit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits. Source data verification (SDV) must be conducted using a GSK standard SDV sampling strategy (as defined at the study start in the study specific monitoring guidelines) in which monitors will perform partial SDV for all subjects and full SDV for selected subjects.

VI. Archiving of Data

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g., microfiche, scanned, electronic for studies with an eCRF, for example); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/ institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/ institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/ institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for GSK or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit drug regulatory agencies and GSK audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application, Biologics Licensing Application.

Having the highest quality data and studies are essential aspects of vaccine development. GSK has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and

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consistency. In addition, Regulatory Compliance assures that GSK Biologicals' sponsored studies are in accordance with GCP and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. GSK's audits entail review of source documents supporting the adequacy and accuracy of CRFs, 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 CRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.

GSK Biologicals will gladly help investigators prepare for an inspection.

VIII. Ownership, Confidentiality and Publication

Ownership:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:

Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:

For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least 21 (twenty-one) days [or at least 15 (fifteen) working days for abstracts/posters/presentations]. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

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Appendix C Overview of the Recruitment Plan

- The study will be conducted at multiple sites in Africa. (Amendment 1: 24 August 2005)
- Target enrolment will be 4,800 eligible subjects. (Amendment 6: 2 August 2007)
- As of January 2006 a total of 1,827 subjects have been enrolled in South Africa (Cohort 1 in South Africa). Enrolment in South Africa was suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa shall resume after the RV season to enrol the total planned number of subjects (Cohort 2 in South Africa). (South Africa-specific Amendment 5: 10 July 2006)
- Subjects in Malawi will be enrolled within a period of 6 to 8 months. (Malawi-specific amendment 4: 15 May 2006)
- The intended duration of the study for subjects in Cohort 1 South Africa, per subject, will not exceed a maximum of 10 to 11 months. The intended duration of the study, per subject, will not exceed a maximum of 24 months for subjects in Cohort 2 South Africa and the Cohort in Malawi. (Amendment 6: 2 August 2007)
- The recruitment will be monitored by the site monitor.

Appendix D Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by 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

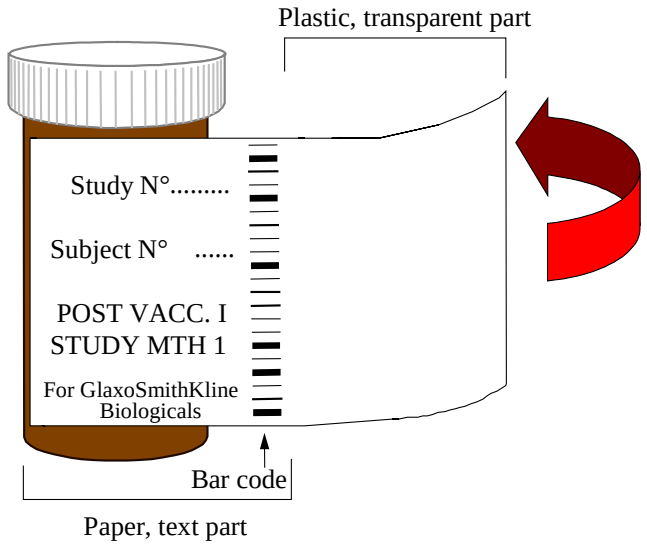
- The standard labels provided by GSK Biologicals should be used to label each serum sample.

- 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 Serum Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. A copy of this list should be retained at the study site, while the original should be sealed in a plastic envelope and shipped with the serum samples.

- Once 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 will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

1. Collection

- Containers and ziplock bags will be provided to parents/guardians for collection of stool samples during any gastroenteritis episodes. Parents/guardians will be asked to preferably use the containers to collect stool samples. If this is not possible, soiled diapers should be individually placed in the ziplock bags and sealed.

2. Labelling

- The parents/guardians/study personnel should complete the label provided on the container/ziplock bag label with a black ink or ballpoint pen and return the collected stool samples to the study personnel.
- If necessary, any hand-written additions to the labels by the study personnel should be made using indelible ink.

3. Preparation of aliquot

- Stool samples collected during specified timepoints and gastroenteritis episodes will be processed, at the study site or designated laboratory, to prepare an aliquot in a 8 ml tube. (South Africa-specific Amendment 5: 10 July 2006)

[1] The Serum Listing Form and the Specimen Transfer Form are standard documents used in GSK Biologicals' clinical trials. These documents are provided by GSK Biologicals' Clinical Trials' monitor at study initiation.

- After the aliquot to be shipped to GSK Biologicals' is prepared, a back-up sample should be maintained using excess material. (Amendment 2: 27 October 2005)

4. Sorting and storage

- The 8 ml tubes with stool specimens should be stored at a temperature between -20°C and -70°C until shipment to GSK Biologicals. Wherever possible, a backup facility for storage of stool samples should be available.
- The back-up sample should be stored at a temperature between -20°C and -70°C at least until arrival of the shipped sample at GSK Biologicals, Rixensart has been confirmed. (Amendment 2: 27 October 2005)
- A standard Stool Listing Form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. A copy of this list should be retained at the study site, while the original should be sealed in a plastic envelope and shipped with the serum samples.
- Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to GSK Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.[2]

Please refer to the GSK contact information mentioned above for serum samples.

[2] The Stool Listing Form and the Specimen Transfer Form are standard documents used in GSK Biologicals' clinical trials. These documents are provided by GSK Biologicals' Clinical Trials' monitor at study initiation.

Appendix E Shipment of All Biological Samples

Instructions for Shipment of All Biological Samples

All biological samples should be sent to GSK Biologicals at regular intervals. The frequency of shipment of samples should be decided upon by the Site Monitor, Central Study Coordinator and the investigator prior to the study start.

All biological samples should always be sent by air, preferably on a Monday, Tuesday or Wednesday, unless otherwise requested by the sponsor.

All biological samples must be placed with dry ice (maximum -20°C) in a container complying with International Air Transport Association (IATA) requirements. The completed standard serum 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

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, Reisinger K et al. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet 1999;354:287-90.

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Stool assays

1. Antigen Detection in Stool Samples

Rotavirus antigen in stool samples collected during gastroenteritis episodes will be detected by ELISA at Central Lab (GSK or designated laboratory).

2. RV strain typing

Targeted RV gene will be amplified by Reverse Transcriptase Polymerase Reactions (RT-PCR) to generate RV cDNA fragments. The genotype will be confirmed by hybridization using serotype-specific DNA probes and/or by direct sequencing of the amplified RV cDNA product.

This serotyping analysis can be completed with the determination of the P-serotype which is related to the VP4 gene. In that case, the typing approaches will be based on the methods such as described for the G typing.

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Appendix G Vaccine supplies, packaging and accountability

1. Vaccine and/or other supplies

(Amendment 1: 24 August 2005)

GSK Biologicals will supply the following study vaccines, sufficient number of doses to administer to all subjects as described in the present protocol and including 5% over-randomisation.

- 9,930 doses of the HRV vaccine in monodose vials.
- 7,944 doses of the placebo for HRV vaccine in monodose vials.
- 17,874 doses of the diluent (calcium carbonate buffer) pre-filled syringes.

In addition, at least 5% of placebo and HRV doses will be supplied for replacement of study vaccines in case of breakage, bad storage conditions or any other reason that would make Dose 1 of the study vaccine unusable (i.e. given by mistake to another subject).

At least an additional 5% of study vaccine doses will be supplied for replacement of study vaccines in case of breakage, bad storage conditions or any other reason that would make Doses 2 or 3 of the study vaccine unusable (i.e. given by mistake to another subject).

All monodose vials/pre-filled syringes must be accounted for on the form provided.

In South Africa, sufficient doses of GSK Biologicals' OPV and DTPw-HB/Hib vaccines will be also provided to administer 3 doses of routine vaccines. In Malawi, local EPI vaccinations (OPV and DTPw-HB/Hib) will be used. At least an additional 5% doses will also be supplied in case of breakage. (Amendment 2: 27 October 2005)

Labels for sample identification:
The investigator will receive labels from GSK Biologicals to identify samples taken from each subject at each timepoint. Each label will contain the following information: study number, identification number for the subject (e.g., subject number), sampling timepoint (e.g., post vacc 2), timing (e.g., study Month 4), biological specimen (e.g. serum / GE stool).

Other supplies provided by GSK Biologicals:
In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:

- material for blood collection,
- material for stool samples.

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study.

It is NOT permitted to use any of the supplies provided by GSK Biologicals for purposes other than those specified in the protocol.

2. Vaccine packaging

The vaccines will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number (or numbers, when double-blind), instructions for vaccine administration and any other relevant regulatory requirements.

3. Vaccine shipment from GSK Biologicals Rixensart to local country medical department, dispatching centre or investigational site and from local country medical department to investigational site

On arrival of vaccine shipment, the cold-chain monitoring device should be removed from the vaccine boxes and checked. The temperature recording chart (chart from Cox recorder or print-out data of the electronic device) should be obtained from the temperature recording device.

The following documents should be completed and returned to GSK Biologicals on reception of vaccine shipment:

Notification of vaccine delivery/temperature control
Temperature recording (chart).

These documents should then be returned to:

Attention of Clinical Trials Supply Unit
Clinical Operations Logistics
GSK Biologicals Rixensart
Fax : [redacted]
E-mail: [redacted]

In case of any temperature deviation, the official 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.

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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.

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Appendix H Standard Questionnaire for Verbal Autopsy

Reference: World Health Organisation. A Standard Verbal Autopsy Method for Investigating Causes of Death in Infants and Children. Geneva: World Health Organisation, 1999:1-78, (WHO/CDS/CSR/ISR/99.4)

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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.

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Annex 1 **Letter on WHO's position on use of live vaccines addressed to the Medicines Control Council on September 26, 2004 by WHO officer Professor** [redacted]

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Téléphone Central/Exchange: [redacted]
Direct:
Email:

In reply please refer to:
Prière de rappeler la référence:

Dr [redacted]
The Registrar of Medicines
Medicines Control Council
Department of Health
Private Bag x828
Pretoria
0001

Your reference: **N2/19/8/2**
Votre référence: **MCC Trial Reference No: 20030913**

26 September 2004

Dear Dr [redacted]

444563/022 (Rota-022)

A phase II, double blind, randomised, placebo-controlled study to assess the safety, reactogenicity and immunogenicity of three doses of GSK Biologicals oral live attenuated human rotavirus vaccine (RIX4414 at $10^{6.5}$ $CCID_{50}$) administered to *human immunodeficiency virus (HIV) infected infants at 6, 10 and 14 weeks in South Africa.*

Please find enclosed the responses to the query raised in your letter dated 20 September 2004, regarding the rotavirus vaccine trial planned in South Africa. In principle, the WHO has a very clear stand on the two issues raised as described below:

1. WHO recommends the routine childhood immunization of HIV-infected infants (with reservation only in two special circumstances)
2. WHO regards as a priority the development of a rotavirus vaccine for infants in developing countries

Use of Immunization in HIV-infected infants
The CT committee is correct in that there is an increasing volume of information on the use of the routine childhood vaccines in HIV-infected infants. However, two excellent reviews have recently been published which address the queries raised by the CTC (Moss *et al, Bull WHO* 2003; 81: 61-70; Obaro *et al, Lancet Infect Dis* 2004; 4: 510-518).

The manuscript by Moss *et al*, specifically addresses the WHO / UNICEF recommendations and guidelines for the use of routine immunization in HIV-infected infants (attached file). In essence there are three potential concerns regarding routine childhood immunization of an HIV-infected infant, which are:

- Will the effectiveness of a vaccine be impaired because of underlying immune deficiency?
- Are persons receiving a live viral or bacterial vaccine subject to significantly increased risk compared with non-infected persons?
- Does administering a vaccine significantly affect the rate of HIV-associated disease?

The WHO /UNICEF guidelines and recommendations currently, are to continue to immunize infants in the EPI schedule, as included in the attached document from the WHO webpage (www.who.int/vaccines-diseases/diseases/HIV.shtml), which gives the following responses to the first two questions raised above:

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- *"Most HIV-infected children have the capacity to mount both cellular and humoral immune responses during the first two years of life; decline in these responses occurs during the next two years. Studies of the immunogenicity of the EPI-recommended vaccines have shown satisfactory seroconversion rates in the early stages of the infection"* (page 1, paragraph 3)
- *"To date, there has been no reported increase of adverse events in HIV-infected persons to the live oral polio and measles vaccines, nor to DPT and hepatitis B vaccines, which contain no live organisms"* (page 1, paragraph 1)

The WHO / UNICEF position on the immunization of HIV-infected infants, or infants born to HIV-positive mothers (http://whqlibdoc.who.int/hq/1995/WHO_EPI_GEN_95.03_ev.1.pdf) supports the routine immunization of infants during the EPI schedule with the exception of BCG or live attenuated yellow fever vaccines, should the infant be symptomatic of the HIV disease. In brief, the WHO policy is based on the potential severity of the vaccine-preventable diseases in HIV-infected children, on vaccine safety and immunogenicity and on the degree of HIV-induced immunosuppression in infants this young.

The reviews by Moss *et al* and Obaro *et al*, give detailed descriptions of the vaccine trials forming the basis of the WHO /UNICEF recommendations and responses to all three questions noted above. In particular it is important to note the following comment on the third area of concern:

- *"Importantly, no investigators have observed prolonged elevation of HIV RNA viral load, decreased CD4+ lymphocytes or accelerated HIV disease progression following immunisation"*(Moss *et al*, *Bull WHO* 2003; 81:61-70; Tovo *et al*, *Vaccine* 2000; 18: 1203-09).

Public Health Importance of Rotavirus Vaccines
Rotavirus is the single most important agent associated with severe dehydrating diarrhoeal disease in young children and is associated with approximately 500,000 deaths each year in infants and young children. Due to this high mortality and morbidity, rotavirus vaccines have received international public health prioritisation over the past two decades by the WHO (*WER* 1999; 74: 33-40) and by the Global Alliance of Vaccines and Immunization (GAVI).

There is a clear need for a rotavirus vaccine which should be administered early in life and concomitant with the EPI schedule. Several rotavirus vaccine candidates are under development including two that are close to international licensure (Merck and GSK Biologicals). Before a global recommendation could be made by the WHO and the international community, it has been deemed important to ascertain the safety of the vaccine in HIV-infected infants. This can only be done in a clinical trial setting where the safety of the subjects can be monitored very closely.

Therefore the public health importance of this trial is very high and is required to determine whether a rotavirus vaccine can be implemented into the EPI schedule for infants worldwide.

I trust that this addresses the questions that have been raised.

Yours sincerely

[redacted]

Dr [redacted]
Initiative for Vaccine Research

Annex 2 HIV testing guidelines in children from South Africa

(Amendment 1: 24 August 2005) (South Africa-specific Amendment 5: 10 July 2006)

Source: ***Guidelines for the Management of HIV-infected Children 2005***. Accessed on the website ***http://www.doh.gov.za/docs/factsheets/guidelines/hiv/index.html***.

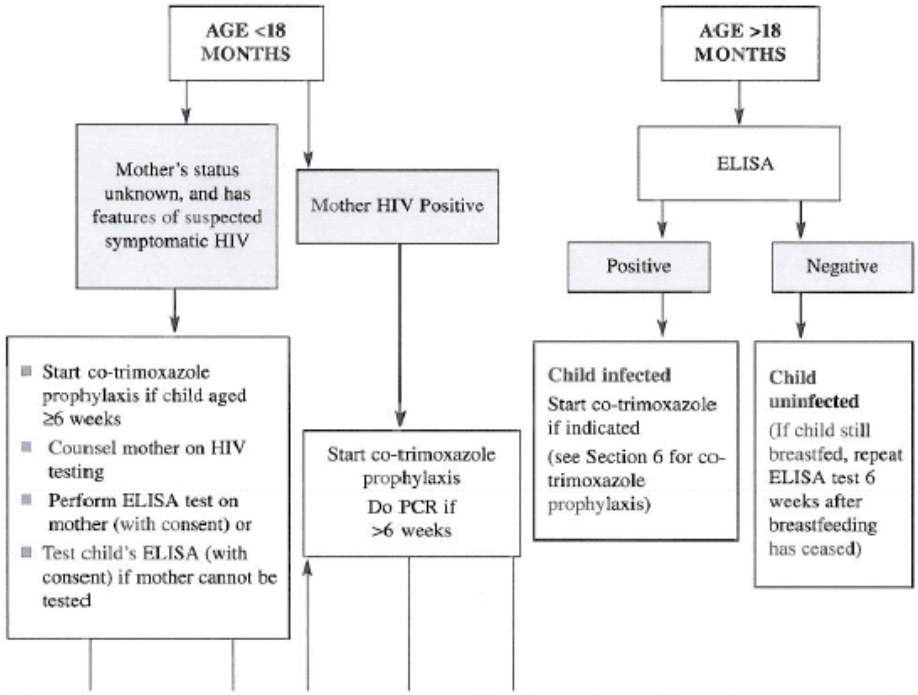
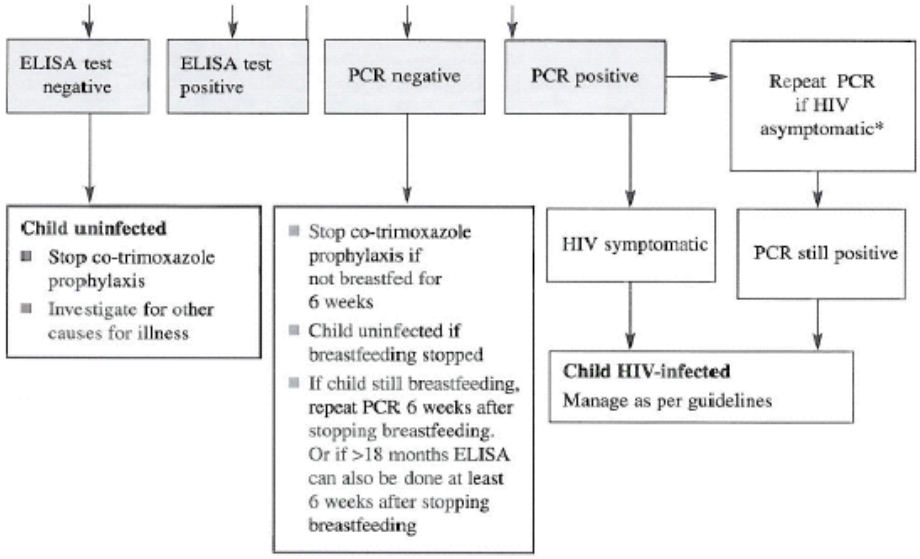


Figure 1: HIV testing guidelines



Note: *Contact laboratory if results are discrepant.
PCR testing may not be available at all centres immediately.
In the absence of PCR, perform HIV ELISA testing at 12 and, if positive, at 18 months.
PCR = HIV DNA PCR
ELISA = HIV ELISA

Annex 3 **Study procedures for cohort 1 enrolled in South Africa as per Amendment 2 dated 27 October 2005** (South Africa-specific Amendment 5: 10 July 2006)

Outline of study procedures for cohort 1 in South Africa

Table 1 **List of study procedures for cohort 1 in South Africa**

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 3.5**	**1 year of age**
Sampling timepoint	**Pre**		**Post vacc 2**	**Post vacc 3**		
Informed consent	•					
Informed consent addendum for HIV testing			•			
Medical history	•					
Medical history for HIV	#		•			
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•		•
Check of contraindications	•	•	•			
Randomisation	•					
Physical examination	•	#	#	#		#
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•			•		•
Blood sampling						
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects		
For HIV testing			• (3 ml in South Africa) in subjects whose parent/ guardian has given consent at Visit 3	• (2 ml in South Africa) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test		
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•
Study vaccination (HRV or placebo)	•	•	•			
Routine EPI vaccination	•	•	•			
Recording of AEs leading to drop-out	•	•	•	•		•
Return of completed diary cards by parents/guardians		•	•	•		•
Diary card transcription		•	•	•		•

Age	5-10 weeks					
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6
Timing	Day 0	Month 1	Month 2	Month 3	Month 3.5	1 year of age
Sampling timepoint	Pre		Post vacc 2	Post vacc 3		
Recording concomitant medication/vaccination	•	•	•	•		•
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•
Record results of HIV testing			•	•		
Inform subjects of HIV result				•	•	
Record results of HIV testing after breast feeding ceases						•
Study Conclusion						•

†Only in subjects with confirmatory HIV test

• is used to indicate a study procedure which requires documentation in the individual CRF.

* = The blood sample will be collected before administering the dose of vaccine/placebo.

is used to indicate a study procedure which does not require documentation in the individual CRF.

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

Table 2 Intervals between study visits for cohort 1 in South Africa

Interval	Size of interval
1 (Visit 1→Visit 2)	28 to 48 days
2 (Visit 2→Visit 3)	28 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days
4 (Visit 4→Visit 5)	7 to 48 days
Visit 6	343-391 days of age

Detailed description of study visits for cohort 1 in South Africa

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- Written informed consent from the parent/guardian of the subject.
- Medical history taking.
- Check of inclusion/exclusion criteria.
- Check contraindications to vaccination.
- HBV, BCG and OPV doses administered at birth should be recorded in the CRF. Record any prior/concomitant vaccinations administered in the CRF.

- Randomisation (or subject) number attribution.
- Physical examination and recording of height and weight.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Collection of pre-vaccination blood sample for serology from a subset of 570 subjects:

In South Africa, a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Vaccination:

Oral administration of Dose 1 of the HRV vaccine or its placebo.

Administration of Dose 1 of the routine EPI vaccine (DTPw-HB/Hib and OPV) in all groups.

All vaccines should be administered according to the guidelines set out in Section 6.2. All administered vaccines should be recorded in CRF.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 2. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.

- Parents/guardians will be instructed to attend the local hospital, close to the site of the clinics for after-hours consultation.

Visit 2, Month 1, Dose 2 (*28*-48 days after Visit 1)

- Physical examination.
- Check of elimination criteria.
- Check contraindications to vaccination.
- Recording of SAEs that may have occurred since the previous visit.
- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Return any stool samples.
- Record AEs leading to drop-out in the CRF.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Vaccination:

Oral administration of Dose 2 of the HRV vaccine or its placebo.

Administration of Dose 2 of the routine EPI vaccine (DTPw-HB/Hib and OPV) in all groups.

All vaccines should be administered according to the guidelines set out in Section 6.2. All administered vaccines should be recorded in CRF.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 3. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.

- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.

Visit 3, Month 2, Dose 3 (*28*-48 days after Visit 2)

- Physical examination.
- Check of elimination criteria.
- Check contraindications to vaccination.
- Recording of SAEs that may have occurred since the previous visit.
- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Return any stool samples.
- Record AEs leading to drop-out in the CRF.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Record medical history with regards to HIV exposure in the CRF. (Amendment 1: 24 August 2005)
- Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.
- Collection of whole blood ***(***3 ml ***in South Africa)*** for HIV testing from subjects whose parents/guardians gave consent.

When materials are provided by GSK Biologicals or designated laboratory, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Record results of the HIV test at Visit 3 in the CRF.
- Pre-vaccination assessment of axillary or rectal body temperature (Temperature ≥ 37.5°C axillary or ≥ 38.0°C rectally warrants deferral of vaccination).
- Vaccination:

Oral administration of Dose 3 of the HRV vaccine or its placebo.

Administration of Dose 3 of the routine EPI vaccine (DTPw-HB/Hib and OPV) in all groups.

All vaccines should be administered according to the guidelines set out in Section 6.2. All administered vaccines should be recorded in CRF.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 4. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.
- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- Physical examination.
- Check of elimination criteria.
- Recording of height and weight.
- Recording of SAEs that may have occurred since the previous visit.
- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Record AEs leading to drop-out in the CRF.
- Return any stool samples.
- Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Collection of a blood sample for serology from all subjects: (Amendment 1: 24 August 2005)

In South Africa, a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.

- Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood (2 ml in South Africa) for a confirmatory HIV test.

When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- Record results of the HIV test at Visit 4 in the CRF.
- A study staff member will visit the parents/guardians weekly until the next study visit to check on the occurrence of any GE.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 6. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.
- Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- Parents/guardians should contact the study physician or study staff if the child manifests any of these signs or symptoms and that they perceive as serious.
- Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.
- Parents/guardians will be reminded to attend their usual clinic for recommended routine vaccinations (Measles and DTPw/HBV/Hib booster).

Visit 5, Month 3.5, Follow-up (7- 48 days after Visit 4) Only for subjects who needed confirmatory HIV testing

- Communicate HIV test result from Visit 4 to parents/guardians and post-test counselling.

Visit 6, Follow-up (343-391 days of age)

- Physical examination.
- Recording of height and weight.
- Check of elimination criteria.
- Recording of SAEs that may have occurred since visit 4.

- Record any concomitant/intercurrent vaccinations and medications administered in the CRF.
- Record results in the CRF if the HIV test was repeated after breast feeding cessation.
- Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.
- Return any stool samples.
- Record AEs leading to drop-out in the CRF.
- Study conclusion.

Appendix I Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**
Amendment number:	Amendment 1
Amendment date:	24 August 2005
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes:

This protocol was amended on 24 August 2005 to implement the following changes:

- To increase the sample size: The assumed attack rate of 2% for severe RV GE for sample size estimation in the original protocol was found to be too optimistic based on the results obtained in several studies with GSK Biologicals' HRV vaccine. A more conservative attack rate of 1.5% was therefore considered and the sample size was revised.
- In the context of the increased sample size, to specify the target enrolment in South Africa.
- To allow HIV testing according to the national guidelines in south Africa. HIV testing will be perfomed at Visit 3 in all subjects whose parents/guardians gave consent, followed by a confirmatory test at Visit 4 in HIV positive subjects who are asymptomatic.
- To add an additional study visit to communicate results of the confirmatory HIV test to the parents/guradians.
- To change method of data collection from Remote Data Entry to Case Report Forms.
- Following feedback from the ERCs, changes to reflect local clnical practice for care and treatment were made.

Amended text has been included in *bold italics* in the following sections. Deleted text is shown in strikethrough below.

CONFIDENTIAL

Cover page

[redacted] ~~Associate~~ Director

Study title

A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants ~~in South Africa~~.

List of abbreviations

CRF	***Case Report Form***
~~**eCRF**~~	~~**Electronic Case Report Form**~~

Glossary of terms

Rotavirus (RV) GE ***caused by the circulating wild-type rotavirus strain*:**	
RV season ***in South Africa*:**	Based on epidemiological observations in South Africa, the RV season will be considered during the period from March 01 to ~~June 30~~ ***July 31.***

Section 1.1

~~Based on the year 2000 HIV prevalence estimate of 22.9% (95% C.I. 20.1; 25.7%) for adults in the Northwest Province where study rota-014 was conducted and with transmission of HIV from mother to child reported from 20 to 70% in South Africa we estimated that there were about 20 infants who were HIV positive.~~

The 2004 annual antenatal survey indicated that HIV prevalence among pregnant women is 29.5% (CI 28.5% - 30.5%) compared to the 27.9% (CI 26.8% - 28.9%) observed in 2003 [Department of Health, South Africa***,*** 2004***].***

Synopsis (Rationale) and Section 1.2

Continuing evaluation of the HRV vaccine in Africa, this study will evaluate the efficacy, safety and immunogenicity of the HRV vaccine at the selected optimum virus concentration in healthy ~~South~~ African infants when given concomitantly with routine Expanded Program of Immunisation (EPI) vaccines.

- To determine if the GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*. **(Amendment 1: 24 August 2005)**.

Criteria: The primary objective will be reached if the lower limit of the of the 95% CI on vaccine efficacy is >0%.

Refer to Section 10.1 for definition of the primary endpoint.

Synopsis (Primary Objective) and Section 2.1

- To determine if the GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.

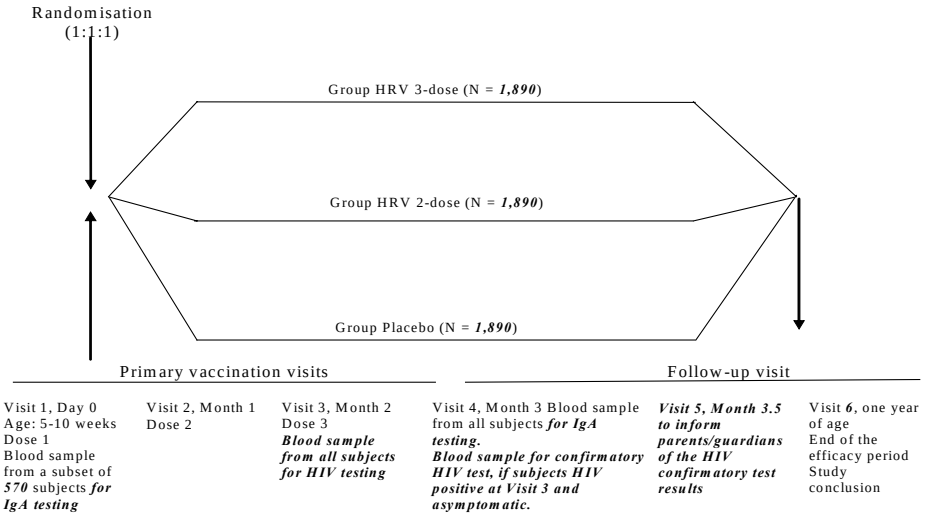
Synopsis (Secondary Objectives) and Section 2.2
Efficacy

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the of HRV vaccine or placebo until Visit ~~5~~***6***.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last

dose of HRV vaccine or placebo until Visit ~~5~~***6*** for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season.

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~***6***.

Section 3



Synopsis (Study design) and Section 3

Group HRV 3-Dose: 3 doses of HRV given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N=~~1,410~~ ***1,890***)

Group HRV 2-Dose: 2 doses of HRV given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose will be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding) (N=~~1,410~~ ***1,890***)

Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N=~~1,410~~ ***1,890***)

- All subjects will have five study visits ***(Visit 1, 2, 3, 4 and 6). Subjects who undergo HIV testing at Visit 4 will have one additional visit (Visit 5):***

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=~~420~~***570***), Dose 1 of HRV vaccine or placebo and routine EPI vaccines.

  Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.***

Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive at Visit 3 and are asymptomatic for a confirmatory HIV test.***

Visit 5 (Month 3.5) Only in Subjects with confirmatory HIV testing at Visit 4 – Inform parents/guardians of the confirmatory HIV test's results and offer further counselling.

Visit ~~5~~ ***6*** (at one year of age) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) and study conclusion.

- Routine EPI schedule vaccinations (~~DTPw-HBV-Hib~~ DTPw-HB/Hib and OPV) should be administered concomitantly with the study vaccine at Visit 1, 2 and 3 following the EPI recommendation (at approximately 6, 10 and 14 weeks of age) and documented in the CRF.
- Recording of height and weight at Visit 1, Visit 4 and Visit ~~5~~***6***.
- Blood samples will be collected from a subset of subjects (N=~~420~~***570*** subjects) at Visit 1 and from all subjects at Visit 4 ***to measure anti-rotavirus IgA antibodies.***

  Blood sample at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at Visit 4 from subjects who test HIV positive at Visit 3 and are asymptomatic.
- Active follow-up for occurrence of GE episodes (diarrhoea) via weekly visit to a subject by study personnel during the entire study period (from the day of Dose 1 until Visit ~~5~~***6***).
- ***Results of HIV testing on blood samples collected at Visit 3 will be communicated to the parents/guardians at Visit 4.*** Pre-test ***and post-test*** counselling will be offered to all mothers or guardians of study subjects ***who consented for HIV testing*** ~~at the centers. Counselling will be offered to mothers or guardians of HIV positive subjects at the centers.~~ ***For subjects who test HIV positive at Visit 3 and are asymptomatic, a confirmatory HIV test should be performed at Visit 4. If a confirmatory HIV test is done, the parents/guardians will have to visit the study site approximately two weeks after Visit 4 (Contact 1) so that the study staff can inform them of the confirmatory HIV test results and offer further counselling. Results of the HIV test should be recorded in the CRF.***

  In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [***National Antiretroviral Treatment Guidelines, First Edition, 2004***] and Standard of Care provided during GSK sponsored trials.

Synopsis (Study design), Abbreviations, Sections 3, 4.3, 5.1.1, 5.2, 5.4, 5.5, 6.2, 6.4.2, 6.6, 6.9, 8.1, 8.4, 8.5, 8.6.1, 8.12, 9.2.1 and 9.2.2.
References to "Remote Data Entry (RDE) and Electronic Case Report Form (eCRF)" replaced with "Case Report Form (CRF)".

Synopsis (Number of subjects)
Total target enrolment will be ***5,670 subjects*** (***1,890 subjects in each group*** ~~4,230 subjects (1,410 subjects in each group~~).

A subset of ~~420~~***570*** subjects will provide a blood sample at Visit 1 and all subjects will provide a blood sample at Visit 4 ***to measure anti-rotavirus IgA antibodies***.

Blood sample at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at Visit 4 from subjects who test HIV positive at Visit 3 and are asymptomatic.

Section 4.1
Total target enrolment will be ***5,670 subjects*** (***1,890 subjects in each group*** ~~4,230 subjects (1,410 subjects in each group~~).

All subjects will be enrolled at multiple sites in ~~South~~ Africa.

A minimum of 2,600 subjects will be enrolled in South Africa. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa.

Enrolment will be terminated when ~~4,230~~ ***5,670*** subjects have been enrolled.

A subset of ~~420~~***570*** subjects will provide a blood sample at Visit 1 ***to measure anti-rotavirus IgA antibodies***. All subjects will provide a blood sample at Visit 4 to assess the immunogenicity of study vaccines ***(anti-rotavirus IgA antibodies)***.

Blood sample at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at Visit 4 from subjects who test HIV positive at Visit 3 and are asymptomatic.

Section 5.1.
When the World Medical Association amended the Declaration in October 2000, GSK, other pharmaceutical companies and other stakeholders who sponsor studies did not accept the literal interpretations of the revised paragraphs 29 and 30. In the case of paragraph 29, we consider that there are situations in which there is a scientific need for a placebo control and in these particular circumstances, this is not intrinsically unethical. Additionally, this aspect of study design will in any case be reviewed by the relevant Ethics Committee.

In the case of paragraph 30, that statement assumed - without reference to the overall stage of development of the experimental product - that the results of individual studies could justify the continued treatment of study subjects with the experimental product

and indeed, oblige sponsors to provide it irrespective of the state of knowledge at that time and of many other important practical issues eg availability of supplies.

These are the reasons for GSK referencing the 1996 version of the Declaration of Helsinki. In the case of this particular study, the changes introduced in 2000 by paragraphs 29 and 30 are not relevant to the design or conduct of this study.

Section 5.1.2

In addition to the Informed Consent Form at Visit 1 to participate in this study, parents/guardians will be presented with a second Informed Consent Form at Visit 3 to obtain consent for HIV testing of the subjects.

Section 5.2

- ***Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit 3.***
- ***Pre-test counselling and informed consent for HIV testing will be performed at Visit 3. A blood sample will be obtained at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on blood samples collected at Visit 3 will be communicated to the parents/guardians at Visit 4. Post-test*** counselling will be offered to mothers or guardians ***of study subjects who consented for HIV testing. For subjects who test HIV positive at Visit 3 and are asymptomatic, a confirmatory HIV test should be performed at Visit 4. If a confirmatory HIV test is done, the parents/guardians will have an additional study visit (Visit 5 approximately 2 weeks after Visit 4) so that the study staff can inform them of the confirmatory HIV test results and offer further counselling. Results of the HIV test should be recorded in the CRF.***

  In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [***National Antiretroviral Treatment Guidelines, First Edition, 2004***] and Standard of Care provided during GSK sponsored trials. GSK Biologicals will facilitate access to ARV treatment centers for any children who test HIV positive at Visit 3, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

- ***If a child develops symptoms indicative of AIDS (WHO stages II or III), or has to be hospitalised before Visit 3, HIV testing and the concerned Informed Consent will be proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatoryHIV test will be performed as necessary.***
- ***National Guidelines in South Africa recommend HIV testing 3 months after breast feeding cessation which usually corresponds to 9 month old. The results of repeat test after breast feeding ceases should be recorded in the CRF.***
- ***As part of the clinical practice at the study site, mothers together with their infants who are HIV positive will be offered support and facilitated access to ARV treatment centers where they will receive prophylaxis and care.***
- ***As part of the clinical practice at the study site, infants who have diarrhoea should be offered care and treatment at the study site during the study.***

- Active surveillance for GE (diarrhoea) will be conducted by the study staff during the entire study period (starting at Dose 1 until Visit ~~5~~***6***).
- Parents/guardians of all subjects will be instructed to collect stool sample(s) if the subject develops diarrhoea at any time until Visit ~~5~~***6***.

Section 5.4

Age	5-10 weeks					
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	*VISIT 5†*	VISIT ~~5~~*6*
Timing	Day 0	Month 1	Month 2	Month 3	Month 3.5	1 year of age
Sampling timepoint	Pre		*Post vacc 2*	Post vacc 3		
Informed consent addendum for HIV testing			•			
Medical history for HIV	#		•			
Blood sampling						
To test anti-rotavirus IgA antibodies	•* (2 ml) in subset (N=***570***)			• (***2*** ml) in all subjects		
For HIV testing			***• (3 ml) in subjects whose parent/ guardian has given consent at Visit 3***	***• (2 ml) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test***		
Record results of HIV testing			•	•		
Inform subjects of HIV result				•	•	
Record results of HIV testing after breast feeding ceases						•

†Only in subjects with confirmatory HIV test

• is used to indicate a study procedure which requires documentation in the individual CRF.

is used to indicate a study procedure which does not require documentation in the individual CRF.

Table 2 Intervals between study visits

Interval	Size of interval
4 (Visit 4→Visit 5)	***7 to 48 days***
Visit ~~5~~***6***	343-391 days of age

Section 5.5

Visit 1, Day 0: 5-10 weeks of age, Dose 1

Administration of Dose 1 of the routine EPI vaccine (~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) in all groups.

Visit 2, Month 1, Dose 2 (30-48 days after Visit 1)

Administration of Dose 2 of the routine EPI vaccine (~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) in all groups.

Visit 3, Month 2, Dose 3 (30-48 days after Visit 2)

- ***Record medical history with regards to HIV exposure in the CRF.***
- ***Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.***
- ***Collection of 3 ml of whole blood for HIV testing from subjects whose parents/guardians gave consent.***

When materials are provided by GSK Biologicals or designated laboratory, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the HIV test at Visit 3 in the CRF.***
- Vaccination:

Administration of Dose 3 of the routine EPI vaccine ~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) in all groups.

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- ***Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling.***
- Collection of a blood sample for serology from all subjects: a minimum of ~~3~~***2*** ml of whole blood to provide a minimum of ~~1.5~~***0.8*** ml of serum according to instructions in Appendix D.
- ***Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of 2 ml of whole blood for a confirmatory HIV test.***
- ***Record results of the HIV test at Visit 4 in the CRF***.
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit ~~5~~***6***.

Visit 5, Month 3.5, Follow-up (7- 48 days after Visit 4) Only for subjects who needed confirmatory HIV testing

- ***Communicate HIV test result from Visit 4 to parents/guardians and post-test counselling.***

Visit ~~5~~ *6*, Follow-up (343-391 days of age)

- Recording of SAEs that may have occurred since ***visit 4***
- ***Record results in the CRF if the HIV test was repeated after breast feeding cessation.***

Section 5.6.2

GE Stool analysis

All stool samples collected during diarrhoea episodes from Visit 1 to Visit ~~5~~ ***6*** will be processed at the study site and shipped frozen to GSK Biologicals, Belgium. If any G1 RV is detected in the stool specimens, vaccine virus ~~will~~ ***may*** be differentiated from the wild type serotype by sequence analysis or an equivalent approach.

Serum analysis

Blood samples collected from a subset of ~~420~~***570*** subjects at Visit 1 and from all subjects at Visit 4 will be centrifuged and the separated serum should be stored at –20°C until shipped to GSK Biologicals, Belgium for analysis.

HIV assay

HIV testing will be done according to the algorithm presented in Figure 1 (see below) based on the guidelines HIV testing guidelines in children from the Department of Health, South Africa [National Antiretroviral Treatment Guidelines, First Edition, 2004] as outlined in Annex 2.

HIV testing at Visit 3 will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at Visit 3 and are asymptomatic, a confirmatory HIV test should be performed at Visit 4.

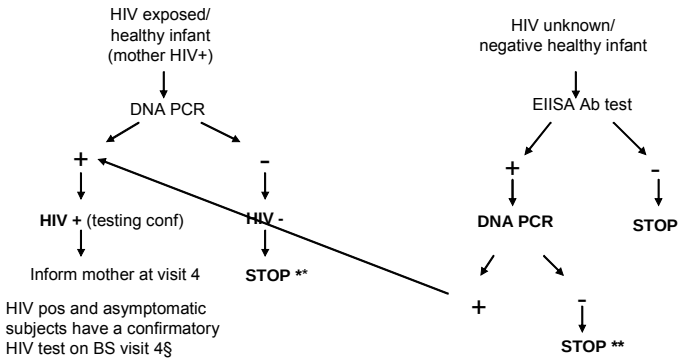
If a child develops symptoms indicative of AIDS (WHO stages II or III), or has to be hospitalised before Visit 3, HIV testing and the concerned Informed Consent will be proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.

National Guidelines in South Africa recommend HIV testing 3 months after breast feeding cessation which usually corresponds to 9 month old. The results of the repeat test after breast feeding ceases in HIV exposed subjects who were negative at visit 3 should be recorded in the CRF.

In case of discrepancy between HIV test results at Visit 3 and Visit 4 (HIV positive at Visit 3, negative at Visit 4), the HIV test should be repeated on the Visit 4 blood sample If the discrepancy remains, the child should be sent to an ARV roll out center for HIV repeat test on a new blood sample according to National Guidelines in South Africa.

HIV tests will be performed locally at designated laboratories accredited for HIV testing and using approved test kits (see last updated version of laboratory workbook for details of blood sample collection, transportation and testing) (~~see laboratory workbook~~).

Figure 3 HIV testing algorithm



* If infant has signs of HIV infection or has to be hospitalized, his HIV status will be done before visit 3
** If breast-feeding : repeat test at 3 months after breast-feeding cessation
§ documented study contact after visit 4

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times from Visit 1 until Visit ~~5~~***6***			RV antigen	All	None
Serum analysis					
Timing	**Month**	**Visit no**			
Pre	Day 0	1	IgA anti-HRV	Subset of ***570*** subjects	None
Post-vacc 3	Month 3	4	IgA anti-HRV	All	None
HIV assay in *subjects whose parent/guardian gave consent*					
Post-vacc 2	***Month 2***	***3***	***Serum*** HIV antibody test ***(ELISA)***	***Subjects not exposed to HIV or HIV status unknown***	None
Post-vacc 2	***Month 2***	***3***	***Whole blood DNA PCR***	***- Subjects not exposed to HIV and positive for HIV antibody*** ***- Subjects exposed to HIV***	None
Post-vacc 3	***Month 3***	***4***	***Whole blood DNA PCR***	***Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic***	***None***

Any additional testing on biological samples to further evaluate the immunogenicity of the ***HRV*** vaccine ***(such as neutralisation assay)*** will be performed if deemed necessary by GSK Biologicals if any findings in the present study necessitate further investigation of the vaccine.

Based on the result of the HIV assay, access to further testing, treatment or counselling will be available ***to subjects in South Africa*** as per the national guidelines in South Africa (also refer to Section 5.2).

Section 6.4
Target enrolment will be ~~4,230 subjects (1,410 subjects in each group)~~ ***5,670 subjects*** (***1,890 subjects in each group***).

Section 6.4.3
The subset of ~~420~~***570*** subjects (~~140~~ ***190*** subjects per group) from selected sites will provide a blood sample at Visit 1.

Section 6.9
Any investigational medication or vaccine administered throughout the study (from Visit 1 to Visit ~~5~~***6***) must be recorded in the CRF.

Any ARV therapy given throughout the study (from Visit 1 to Visit 6) must be recorded in the CRF.

Section 8.5
All AEs leading to subject withdrawal/drop-out during the period starting at Visit 1 and ending at Visit ~~5~~ ***6*** must be recorded in the subject's CRF.

Section 8.6.1
The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for AEs leading to drop-out from Visit 1 to Visit ~~5~~ ***6*** and SAEs reported from Visit 1 to Visit ~~5~~ ***6***. The assessment will be based on the investigator's clinical judgement.

Section 8.11
Informtion on behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

Section 8.12
In south Africa, procedures to be followed for ARV therapy will be in compliance with national guidelines in South Africa [Operational plan for comprehensive HIV and AIDS Care, Management and Treatment for South Africa 19 Nov 2003] and Standard of Care provided during GSK sponsored trials. GSK Biologicals will facilitate access to ARV treatment centers for any children who test HIV positive ~~at Visit 4~~, but decisions towards treatment will be taken by appropriate staff at these treatment centers. Pre-test ***and post-test*** counselling will be offered to all mothers or guardians of study subjects ***who***

consented for HIV testing. ~~Counselling will be offered to mothers or guardians of HIV positive subjects at the centers.~~

Synopsis (Primary Endpoint) and Section 10.1

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains in pooled HRV groups versus the placebo group during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

Synopsis (Secondary Endpoints) and Section 10.2
Efficacy

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6*** for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

Section 10.3
~~A total of 4,230 subjects (1,410 subjects in each group) will be enrolled. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 3,600 evaluable subjects (1,200 subjects in each group) are expected to be evaluable for the analysis of the primary objective.~~

~~Considering a 1:1:1 randomisation ratio and various incidence rates expected in the study, Table 5 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy.~~

~~Assuming a 2% incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of 3,600 evaluable subjects has 80%~~

~~power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).~~

~~Table 7 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,200 evaluable subjects, N HRV pooled groups = 2,400 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 5~~			
	~~60%~~	~~70%~~	~~80%~~	~~90%~~
~~1%~~	~~46%~~	~~65%~~	~~82%~~	~~95%~~
~~2%*~~	~~80%~~	~~94%~~	~~99%~~	~~100%~~
~~3 %~~	~~94%~~	~~99%~~	~~100%~~	~~100%~~

~~*Anticipated incidence rate (reference: Study rota-013)~~

~~Table 6 presents the power to detect a statistically significant difference between each HRV group and placebo group for a range of vaccine efficacy.~~

~~Table 8 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,200 evaluable subjects, N HRV group = 1,200 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 5~~			
	~~60%~~	~~70%~~	~~80%~~	~~90%~~
~~1%~~	~~34%~~	~~50%~~	~~68%~~	~~86%~~
~~2%*~~	~~67%~~	~~84%~~	~~95%~~	~~100%~~
~~3 %~~	~~85%~~	~~96%~~	~~100%~~	~~100%~~

~~*Anticipated incidence rate (reference: Study rota-013)~~

A total of 5,670 subjects (1,890 subjects in each group) will be enrolled. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 4,800 evaluable subjects (1,600 subjects in each group) are expected to be evaluable for the analysis of the primary objective.

Considering a 1:1:1 randomisation ratio and various incidence rates expected in the study, Table 5 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy.

Assuming a 1.5% incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of 4,800 evaluable subjects has 80% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).

~~**Table 9 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,600 evaluable subjects, N HRV pooled groups = 3,200 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)**~~

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6*		
	60%	*70%*	*80%*
1%	*60%*	*78%*	*92%*
*1.5%**	*80%*	*93%*	*98%*
2%	*90%*	*98%*	*99%*
3 %	*98%*	*99%*	*100%*

Anticipated incidence rate

Table 6 presents the power to detect a statistically significant difference between each HRV group and placebo group for a range of vaccine efficacy.

Table 10 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,600 evaluable subjects, N HRV group = 1,600 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6*		
	60%	*70%*	*80%*
1%	*46%*	*64%*	*82%*
*1.5%**	*66%*	*84%*	*95%*
2%	*80%*	*93%*	*98%*
3 %	*93%*	*99%*	*99%*

Anticipated incidence rate

Section 10.6

Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit ~~5~~ ***6*** at the end of the efficacy follow-up period.

Section 10.6.1

HIV ~~seropositivy~~ status at ***Visit 3 and*** Visit 4 will be presented.

Section 10.6.2

- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

- Severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6*** for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

The primary objective will be reached if the lower limit of the 95%CI on vaccine efficacy for pooled HRV groups against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6*** is >0%.

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE requiring hospitalisation, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, time to events analysis, ***efficacy against severe RV GE using alternative scoring systems other than the Vesikari system***).

Section 10.6.3
Exploratory safety analyses will be performed according to the HIV seropositivy status ~~at Visit 4~~.

The height and weight increase from Visit 1 to Visits 4 ***and 6*** will be summarised by group.

Appendix B
Instructions for Remote Data Entry replaced with Instructions for Case Report Form.

Appendix C
- The study will be conducted at multiple sites in ~~South~~ Africa.
- Target enrolment will be ~~4,230~~ ***5,670*** eligible subjects.
- Recruitment will be terminated when ~~4,230~~ ***5,670*** eligible subjects have been enrolled.
- ***A minimum of 2,600 subjects will be enrolled in South Africa. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa.***

Appendix G

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 ***and including 5% over-randomisation.***

- ~~7,050~~ ***9,930*** doses of the HRV vaccine in monodose vials.
- ~~5,640~~ ***7,944*** doses of the placebo for HRV vaccine in monodose vials.
- ~~12,690~~ ***17,874*** doses of the diluent (calcium carbonate buffer) pre-filled syringes.

Sufficient doses of GSK Biologicals' OPV ***and DTPw-HB/Hib vaccines*** will be also provided to administer 3 doses of routine vaccines.

Annex 2

Annex 2 outlining the HIV testing guidelines in children was added.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes: The following administrative changes were made to the protocol on 22 September 2005 as per the request of the [redacted]:

- Declaration of Helsinki version 2004 will be used for this study instead of the 1996 version
- A summary of the Informed Consent will be used for better comprehension of the informed consent .
- A questionnaire will be used to monitor parent's/guardian's comprehension of the informed consent.

Amended text has been indicated in bold italics in the following sections:

Section 5.1

The study will be conducted according to Good Clinical Practice (GCP), the ~~1996~~ ***2004*** Declaration of Helsinki (Protocol Appendix A) and local rules and regulations of the country.

~~***When the World Medical Association amended the Declaration in October 2000, GSK, other pharmaceutical companies and other stakeholders who sponsor studies did not accept the literal interpretations of the revised paragraphs 29 and 30. In the case of paragraph 29, we consider that there are situations in which there is a scientific need for a placebo control and in these particular circumstances, this is not intrinsically unethical. Additionally, this aspect of study design will in any case be reviewed by the relevant Ethics Committee.***~~

~~***In the case of paragraph 30, that statement assumed - without reference to the overall stage of development of the experimental product - that the results of individual studies***~~

~~***could justify the continued treatment of study subjects with the experimental product and indeed, oblige sponsors to provide it irrespective of the state of knowledge at that time and of many other important practical issues eg availability of supplies.***~~

~~***These are the reasons for GSK referencing the 1996 version of the Declaration of Helsinki. In the case of this particular study, the changes introduced in 2000 by paragraphs 29 and 30 are not relevant to the design or conduct of this study.***~~

Section 5.1.2
In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the ~~1996~~ ***2004*** Declaration of Helsinki.

An investigator or designate will describe the protocol to potential subjects' parents/guardians face to face. ***At the request of the [redacted], potential subjects' parents/guardians will receive a summary document with the gist of the Informed Consent Form to aid comprehension.***

At the request of the [redacted], all parents/guardians will have to complete an Informed Consent Feedback Form. The responses of the parents/guardians to the questions in the Informed Consent Feedback Form will allow the person taking informed consent to understand what has or has not been understood by the subjects' parents/guardians. In case of incorrect responses, the informed consent will be explained again to the parents/guardians and the investigator or his delegate will assess comprehension. Responses from parents/guardians of the first 50 subjects will be transmitted to the [redacted].

Appendix A
The 1996 Declaration of Helsinki was replaced with the 2004 Declaration of Helsinki.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Amendment number:	Amendment 2
Amendment date:	27 October 2005
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: The protocol was amended on 27 October 2005 to allow participation of a second country, Malawi, in this study. Following addition of Malawi, some country-specific changes were made. Some administrative sections were updated.	

Amended text has been indicated in bold italics in the following sections:

Cover page
[redacted]***Clinical Development Manager***

Investor Agreement

- That I am thoroughly familiar with the appropriate use of the vaccine, as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), ***and*** prescribing information (in the case of a marketed vaccine) ~~and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine)~~.

Glossary of terms

RV season in Malawi:	***The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. (Amendment 2: 27 October 2005)***

Synopsis (Secondary Objectives), Section 2.2

- ***In South Africa,*** to assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2

weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season.

Synopsis (Definitions)

- RV season ***in South Africa***: Based on epidemiological observations, the RV season will be considered during the period from March 01 to June 30 in South Africa.
- ***RV season in Malawi: The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year.***

Synopsis (Study design), Section 3

- Experimental design: Double-blind, randomised, placebo- controlled, multi-center, ***multi-country*** study with three parallel groups.

  In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] and Standard of Care provided during GSK sponsored trials.

Section 1.1

In South Africa, the disease was shown to be seasonal with a clear peak in autumn winter season [Steele , 2003]. ***In Malawi, RV is responsible for a third of outpatient attendances and hospital admissions for acute GE among children under 5 years of age [Cunliffe, 2001]. More than 80% of RV GE cases occur in infants less than one year of age. In Malawi, RV is identified throughout the year; diarrhoeal disease of all causes is most common during the warm, rainy season (November-March), but the proportion of diarrhoeal episodes attributed to RV is greatest during the cooler, dry season (May-September) [Cunliffe 2001 thesis]. The impact of RV season in Malawi is minimal. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. Recently, the greater diversity of RV serotypes in some African countries has been recognised. In particular, serotypes G8 and P[6] have been documented in multiple settings, and in Malawi serotype G8 has comprised approximately 30% of all RV serotypes [Cunliffe, 1999; Cunliffe, 2001].***

As of ~~31 October 2004~~ ***15 July 2005***, the safety database for GSK Biologicals' HRV vaccine contains ~~80,383~~ ***89,243*** subjects. Up to ~~31 October 2004~~***15 July 2005***, ~~3,937~~ ***5,782*** subjects have reported a total of ~~4,525~~ ***6,872*** SAEs. Of these, a total of ~~59~~ ***67*** SAEs have been considered as possibly related by the investigators or with unknown relationship.

Section 4.1 and Appendix C

A minimum of 2,600 subjects will be enrolled in South Africa ***and 3070 subjects will be enrolled in Malawi***. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa ***and a minimum of 2670 subjects to be enrolled in Malawi***.

Section 4.2

- Birth weight > 2000 g ***or if weight unknown, gestation period > 36 weeks.***

Section 5.2

- ***In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] and Standard of Care provided during GSK sponsored trials.***
- National Guidelines in South Africa recommend HIV testing 3 months after breast feeding cessation which usually corresponds to 9 month old. The results of repeat test after breast feeding ceases in HIV exposed subjects ***in South Africa*** who were negative at Visit 3 should be recorded in the CRF.

Section 5.4

Table 1 List of study procedures

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 3.5**	**1 year of age**
Sampling timepoint	**Pre**		**Post vacc 2**	**Post vacc 3**		
To test anti-rotavirus IgA antibodies	•* (2 ml ***in South Africa and 1 ml in Malawi***) in subset (N=570)			• (2 ml ***in South Africa and 1 ml in Malawi***) in all subjects		
For HIV testing			• (3 ml ***in South Africa and 1 ml in Malawi***) in subjects whose parent/ guardian has given consent at Visit 3	• (2 ml ***in South Africa and 1 ml in Malawi***) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test		

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries.

Table 2 Intervals between study visits

Interval	**Size of interval**
1 (Visit 1→Visit 2)	~~**30**~~ ***28*** to 48 days
2 (Visit 2→Visit 3)	~~**30**~~***28*** to 48 days

Section 5.5

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- Collection of pre-vaccination blood sample for serology from a subset of 570 subjects:

In South Africa, a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.

In Malawi, a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.

Visit 2, Month 1, Dose 2 (~~30~~ *28*-48 days after Visit 1)

Visit 3, Month 2, Dose 3 (~~30~~ *28*-48 days after Visit 2)

- Collection of whole blood ***(***~~of~~ 3 ml ***in South Africa and 1 ml in Malawi)*** for HIV testing from subjects whose parents/guardians gave consent.

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- Collection of a blood sample for serology from all subjects:

In South Africa, a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.

In Malawi, a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.

- Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood ***(***2 ml ***in South Africa and 1 ml in Malawi)*** for a confirmatory HIV test.

Section 5.6.1
Back-ups of stool samples will be maintained (see Appendix D) and should be used only for additional shipments in case mailed samples are lost.

Section 5.6.2

HIV assay

South Africa

Figure 1 Algorithm for HIV testing in South Africa

** ***In South Africa:*** If breast-feeding : repeat test at 3 months after breast-feeding cessation

Malawi

For all subjects whose parents gave consent for HIV testing, HIV status will be determined by employing 2 commercially available rapid HIV antibody tests, currently

in use by the Malawi's HIV-testing program (Determine and Unigold). Discrepant HIV results will be verified by PCR testing. When rapid HIV antibody test results are positive, PCR testing will be done. Subjects who test HIV positive at Visit 3 and are asymptomatic will undergo PCR testing at Visit 4.

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times from Visit 1 until Visit 6			RV antigen	All	None
Serum analysis					
Timing	**Month**	**Visit no**			
Pre	Day 0	1	IgA anti-HRV	Subset of 570 subjects	None
Post-vacc 3	Month 3	4	IgA anti-HRV	All	None
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
Post-vacc 2	Month 2	3	Serum HIV antibody test (ELISA)	Subjects not exposed to HIV or HIV status unknown	None
Post-vacc 2	Month 2	3	Whole blood DNA PCR	- Subjects not exposed to HIV and positive for HIV antibody - Subjects exposed to HIV	None
Post-vacc 3	Month 3	4	Whole blood DNA PCR	Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic	None
Malawi					
Post-vacc 2	***Month 2***	***3***	***rapid HIV antibody tests***	***All***	***None***
Post-vacc 2	***Month 2***	***3***	***Whole blood DNA PCR***	***Subjects positive by rapid HIV antibody tests or in case of discrepancy***	***None***
Post-vacc 3	***Month 3***	***4***	***Whole blood DNA PCR***	***Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic***	***None***

In South Africa, based on the result of the HIV assay, access to further testing, treatment or counselling will be available to subjects in South Africa as per the national guidelines in South Africa (also refer to Section 5.2).

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] (also refer to Section 5.2).

Section 8.8.2

The Study Contacts per country (where available) are provided as a separate protocol attachment (refer to Attachment 1); in the case where the Study Contact is not available, you must contact the back-up Study Contact (see below).

~~Study Contact for Reporting SAEs~~
~~Dr.~~ [redacted] ~~Tel:~~ [redacted] ~~Cell:~~ [redacted] ~~Fax:~~ [redacted] [redacted] ~~Tel:~~ [redacted] ~~Cell:~~ [redacted] ~~Fax:~~ [redacted]

Section 8.12

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] and Standard of Care provided during GSK sponsored trials.

Synopsis (Secondary endpoints), Section 10.2

- ***In South Africa,*** occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.

Section 10.6.2

- ***In South Africa, s***evere RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.

Appendix D

Instructions for Handling of Stool Samples

3. Preparation of aliquot

- ***After the aliquot to be shipped to GSK Biologicals' is prepared, a back-up sample should be maintained using excess material.***

4. Sorting and storage

- ***The back-up sample should be stored at a temperature between -20°C and -70°C at least until arrival of the shipped sample at GSK Biologicals, Rixensart has been confirmed.***

Appendix G

1. Vaccine and/or other supplies

In South Africa, sufficient doses of GSK Biologicals' OPV and DTPw-HB/Hib vaccines will be also provided to administer 3 doses of routine vaccines. ***In Malawi, local EPI vaccinations (OPV and DTPw-HB/Hib) will be used.***

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Malawi-specific Amendment 3
Amendment date:	**22 February 2006**
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: The protocol was amended on **22 February 2006** to implement specific changes for Malawi following ERC review.	

Amended text has been indicated in bold italics in the following sections:

Section 1.1

A recent review estimates that 611,000 (range 454,000–705,000) RV-related deaths occur in children under 5 years of age annually [Parashar, 2006]. From 2000 to 2004, RV was estimated to cause 39% of hospitalisations for childhood diarrhea. ~~It is 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 a total of 440,000-452,000 deaths in children under 5 years of age annually [Parashar , 2003]~~.

Synopsis (Rationale) and Section 1.2

Although this HRV vaccine is registered in Malawi and will become available in the private market; a placebo controlled trial is justified as the vaccine is not available through public health care programmes to the general population. More importantly as the vaccine is not yet recommended in the National Immunisation Guidelines, the data generated in this trial might facilitate evidence-based decisions on population-based vaccine utilisation in the country in particular and the region in general.

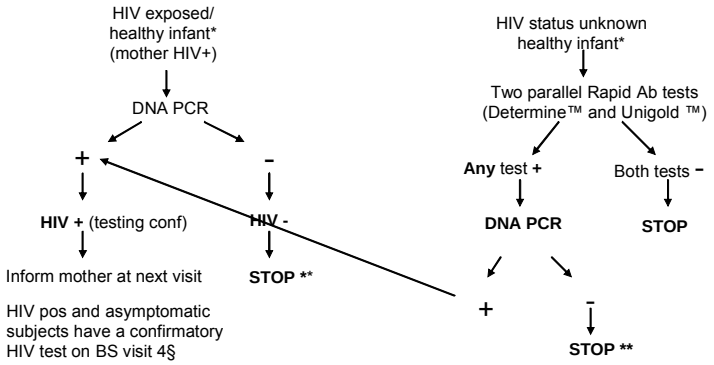
Section 4.2

- ~~Birth weight > 2000 g *or* ***if weight unknown, gestation period > 36 weeks.*** **(Amendment 2: 27 October 2005)**~~

Section 3, Section 5.2, Section 5.6.2 and Section 8.12

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi ~~draft February 2003~~***(1st edition October 2003 or later edition)***] and Standard of Care provided during GSK sponsored trials.

Figure 4 Algorithm for HIV testing in Malawi



* If infant has signs of HIV infection or has to be hospitalized, his HIV status will be done before visit 3
** If breast-feeding : repeat test at 3 months after breast-feeding cessation.
§ documented study contact after visit 4

Section 5.6.2

When ***any of the two*** rapid HIV antibody test results are positive, PCR testing will be done.

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
HIV assay in subjects whose parent/guardian gave consent					
Malawi					
Post-vacc 2	Month 2	3	Whole blood DNA PCR	Subjects positive by ***any of the two*** rapid HIV antibody tests or in case of discrepancy	None

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Malawi-specific Amendment 4
Amendment date:	15 May 2006
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: This Malawi-specific amendment was done on **15 May 2006** to implement the IDMC recommendation dated 03 April 2004.	

Amended text has been indicated in bold italics in the following sections:

Synopsis (Study design) and Section 3

- Study visits: Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). ~~Subjects who undergo HIV testing at Visit 4 will have one additional visit (Visit 5)~~. Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). ***Subjects who undergo the initial HIV testing at Visit 4 may need an additional visit for a confirmatory HIV test (Visit 5 will take place 21-48 days after Visit 4) as well as another contact so that the study staff can inform parents/guardians of the confirmatory HIV test results and offer further counselling.***

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=570) and Dose 1 of HRV vaccine or placebo and routine EPI vaccines. ***Pre-test counselling, informed consent for HIV testing and blood sample from all subjects whose parent/guardian gave consent for HIV testing***.

  Visit 2 (Month 1) – Dose 2 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (adverse events (AEs) leading to drop-out and SAEs). ***Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 1 and collection of an additional blood sample from subjects who test HIV positive at Visit 1 and are asymptomatic for a confirmatory HIV test.***

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102248 (Rota-037) & 111274 (ROTA-037 EXT:Y2)
Administrative Change 2

Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Communication of HIV confirmatory test result and offer further counselling for subjects who had a HIV confirmatory test at Visit 2.***

Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***If HIV test was not performed previously, offer pre-test counselling, informed consent for HIV testing and blood sample for HIV testing, if accepted.***

Visit 5 (Month ***4*** ~~3.5~~) – ***If needed at 21-48 days after Visit 4. Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 4. Collection of an additional blood sample from subjects who test HIV positive at Visit 4 and are asymptomatic for a confirmatory HIV test and planning for informing the parents/guardians about the confirmatory HIV test result in 2 weeks*** ~~only in Subjects with confirmatory HIV testing at Visit 4 – Inform parents/guardians of the confirmatory HIV test's results and offer further counselling~~.

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at the subsequent visit(s) and be performed at any visit up until Visit 4.

- ***Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.***
- ***Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.***
- ***At subsequent visit, inform parents/guardians of the confirmatory HIV test's results and offer further counselling.***

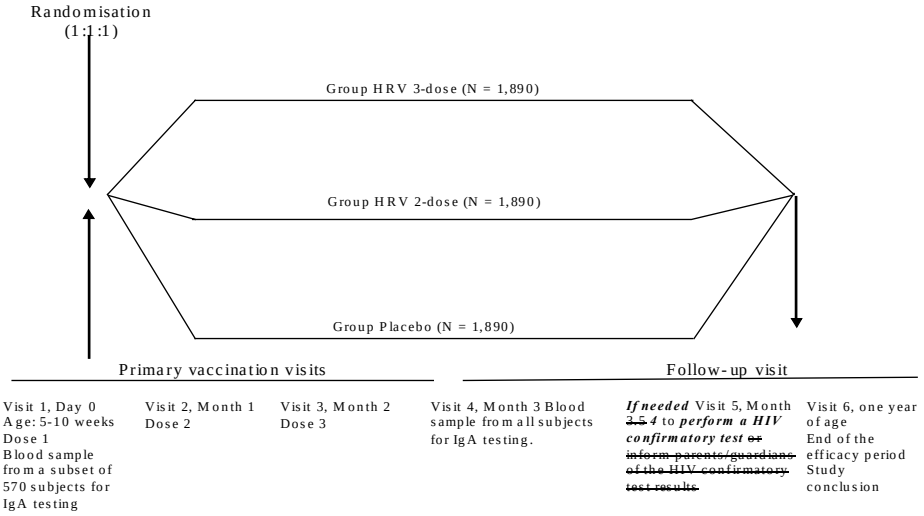
During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing will be proposed at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.

- Blood sample ***will be collected*** from all subjects whose parent/guardian gave ***prior*** consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***at the initial test*** ~~at Visit 3~~ and are asymptomatic.
- Results of HIV testing on blood samples collected ***after informed consent for HIV testing has been obtained*** will be communicated to the parents/guardians at ***the***

subsequent visit. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***at the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. ~~If a confirmatory HIV test is done, the parents/guardians will have an additional study visit (Visit 5 approximately 2 weeks after Visit 4) so that the study staff can inform them of the confirmatory HIV test results and offer further counselling~~. ***Subjects who undergo the initial HIV testing at Visit 4 may need an additional visit for a confirmatory HIV test (Visit 5) as well as another contact so that the study staff can inform parents/guardians of the confirmatory HIV test results and offer further counselling.*** Results of the HIV test should be recorded in the CRF.

- ~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.
- ***The study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health.***

Section 3



Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Blood sample to be collected from all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample at the subsequent visit from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.

Synopsis (Number of subjects) and Section 4.1
Blood sample ~~at Visit 3~~ from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***after the initial test*** ~~at Visit 3~~ and are asymptomatic.

Section 4.1
A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi.

Section 5.2
Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit ~~3~~ ***1.***

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Pre-test counselling and informed consent for HIV testing will be performed. A blood sample will be obtained from all subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on ***collected*** blood samples will be communicated to the parents/guardians at ***the subsequent visit***. Post-test counselling will be offered to mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***after the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. Results of the HIV test should be recorded in the CRF. ~~If a confirmatory HIV test is done, the parents/guardians have to return for Visit 5 (approximately two weeks after Visit 4) so that the study staff can inform them of the HIV test results and offer further counselling.~~ ***Subjects who undergo the initial HIV testing at Visit 4 may need an additional visit for a confirmatory HIV test (Visit 5) as well as another contact so that the study staff can inform parents/guardians of the confirmatory HIV test results and offer further counselling***.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing will be ***proposed at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ~~at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

The study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health.

Section 5.4

Age	5-10 weeks					
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6
Timing	Day 0	Month 1	Month 2	Month 3	Month ~~3~~ *4*	1 year of age
Sampling timepoint	Pre		~~Post vacc 2~~	Post vacc 3		
Informed consent addendum for HIV testing	•		•	•		
Medical history for HIV	#•		•			
For HIV testing, ***if and when accepted‡***	•		~~• (3 ml in South Africa and 1 ml in Malawi) in subjects whose parent/ guardian has given consent at Visit 3~~	~~•• (2 ml in South Africa and 1 ml in Malawi) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test~~		
Confirmatory HIV testing, if required		•			•	
Record results of HIV testing		•	•	•	•	
Inform subjects of HIV result		•	•	•	•	

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries ***(See Section 0 and Section 5.6.2).***

†***Visit 5 will take place 21-48 days after Visit 4 o***nly in subjects ***needing a*** confirmatory HIV test

‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit.

Table 2 Intervals between study visits

Interval	Size of interval
4 (Visit 4→Visit 5)	***21*** ~~7~~ to 48 days

Section 5.5

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- ***Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.***
- ***Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent.***

When materials are provided by GSK Biologicals or designated laboratory, 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

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Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the HIV test at the subsequent visit in the CRF.***
- ***Only in subjects who test HIV positive at the initial test and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test.***

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the confirmatory HIV test at the subsequent visit in the CRF.***
- ***Communicate HIV test result of the confirmatory HIV test to parents/guardians at the subsequent visit and post-test counselling.***

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- ***Proposal for HIV testing to parents/guardians. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ***Record medical history with regards to HIV exposure in the CRF.***

Visit 2, Month 1, Dose 2 (28-48 days after Visit 1)
(Amendment 2: 27 October 2005)

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling and collection of blood samples for confirmatory HIV test if required.***

Visit 3, Month 2, Dose 3 (28-48 days after Visit 2)
(Amendment 2: 27 October 2005)

- ***If confirmatory HIV test done at the preceding visit, communicate the results of the HIV to parents/guardians, record results of HIV test in the CRF and post-test counselling.***
- ~~Record medical history with regards to HIV exposure in the CRF. (Amendment 1: 24 August 2005)~~

- ~~Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling. (Amendment 1: 24 August 2005)~~
- ~~Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals or designated laboratory, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E. (Amendment 1: 24 August 2005)~~

- ~~Record results of the HIV test at Visit 3 in the CRF. (Amendment 1: 24 August 2005)~~

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- ***Proposal for HIV testing to parents/guardians, if HIV testing not done previously. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ~~Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling. (Amendment 1: 24 August 2005)~~.
- ~~Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.~~

- ~~Record results of the HIV test at Visit 4 in the CRF. (Amendment 1: 24 August 2005)~~

If needed, Visit 5, Month *4* ~~3.5,~~ Follow-up (~~7~~*21*- 48 days after Visit 4) Only for subjects who needed confirmatory HIV testing

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling, collection of blood samples for confirmatory HIV test if required and planning for a contact to inform the parents/guardians about the confirmatory HIV test result in 2 weeks.***

Section 5.6.2

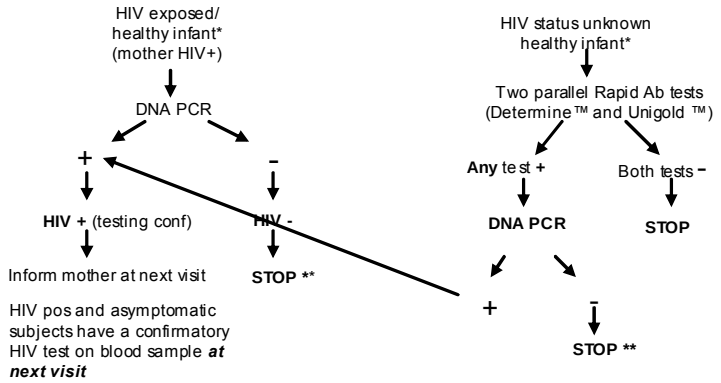
Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

HIV testing ~~at Visit 3~~ will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at ***the initial test*** ~~Visit 3~~ and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit*** ~~Visit 4~~.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing will be ***proposed at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

Malawi

Subjects who test HIV positive at ***the initial test*** ~~Visit 3~~ and are asymptomatic will undergo PCR testing ***at the time of the confirmatory test*** ~~Visit 4~~.



* If infant has signs of HIV infection ***(WHO interim stages III or IV)*** or has to be hospitalised, ***and any HIV testing has not yet been performed***, ***HIV testing and the concerned Informed Consent will be proposed to the mothers***
** If breast-feeding : repeat test at 3 months after breast-feeding cessation.

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
HIV test			Serum HIV antibody test (ELISA)	Subjects not exposed to HIV or HIV status unknown	None
			Whole blood DNA PCR	- Subjects not exposed to HIV and positive for HIV antibody - Subjects exposed to HIV	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic	None
Malawi					
HIV test			rapid HIV antibody tests	All	None
			Whole blood DNA PCR	Subjects positive by any of the two rapid HIV antibody tests or in case of discrepancy	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at ***the initial HIV test*** ~~Visit 3~~ and asymptomatic	None

Section 8.4 and Section 8.7

~~If not yet performed, HIV testing will be encouraged at hospital admission, and the results should be recorded in the CRF. (Amendment 1: 24 August 2005)~~ ***During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing will be proposed by the study staff at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.***

Section 8.12

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

Appendix C

- A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa and a minimum of 2670 subjects to be enrolled in Malawi.
- ~~All subjects will be enrolled within a period of 3 months.~~ ***Subjects in Malawi will be enrolled within a period of 6 to 8 months.***

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	**10 July 2006**
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: This South Africa-specific amendment was done on **10 July 2006** to implement the IDMC recommendation dated 03 April 2004 for the subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa).	

Amended text has been indicated in bold italics in the following sections:

List of abbreviations

PMTCT	***Prevention of Mother To Child Transmission***

Definitions

- RV season in South Africa: Based on epidemiological observations, the RV season will be considered during the period from March 01 to ~~June 30~~ ***July 31*** in South Africa.

Synopsis (Study design) and Section 3

- ***Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa.***
- Study visits: Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). Subjects who undergo ***initial*** HIV testing at Visit 4 will have one additional visit (Visit 5 ***at 21-48 days after Visit 4) to communicate results of the initial HIV test to the parents/guardians. If required, a confirmatory HIV test may be performed at***

Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling.

Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=570 ***Not from cohort 2 in South Africa***) and Dose 1 of HRV vaccine or placebo and routine EPI vaccines. ***Pre-test counselling, informed consent for HIV testing and blood sample from all subjects whose parent/guardian gave consent for HIV testing***.

Visit 2 (Month 1) – Dose 2 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (adverse events (AEs) leading to drop-out and SAEs). ***Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 1 and collection of an additional blood sample from subjects who test HIV positive at Visit 1 and are asymptomatic for a confirmatory HIV test.***

Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Communication of HIV confirmatory test result and offer further counselling for subjects who had a HIV confirmatory test at Visit 2.***

Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***If HIV test was not performed previously, offer pre-test counselling, informed consent for HIV testing and blood sample for HIV testing, if accepted.***

Visit 5 (Month ***4*** ~~3.5~~) – ***At 21-48 days after Visit 4, o***nly in subjects with ~~confirmatory~~ ***initial*** HIV testing at Visit 4***. Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 4. Collection of an additional blood sample from subjects who test HIV positive at Visit 4 and are asymptomatic for a confirmatory HIV test and planning for informing the parents/guardians about the confirmatory HIV test result in 2 weeks***. ~~– Inform parents/guardians of the confirmatory HIV test's results and offer further counselling~~. (Amendment 1: 24 August 2005)

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- ***Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.***
- ***Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.***

- ***At subsequent visit/contact, inform parents/guardians of the confirmatory HIV test's results and offer further counselling.***

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.

- Blood samples will be collected from a subset of subjects (N=570 subjects; ***not from subjects in cohort 2 in South Africa***) at Visit 1 and from all subjects at Visit 4 to measure anti-rotavirus IgA antibodies.
- Blood sample ***will be collected*** from all subjects whose parent/guardian gave ***prior*** consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***at the initial test*** ~~at Visit 3~~ and are asymptomatic.

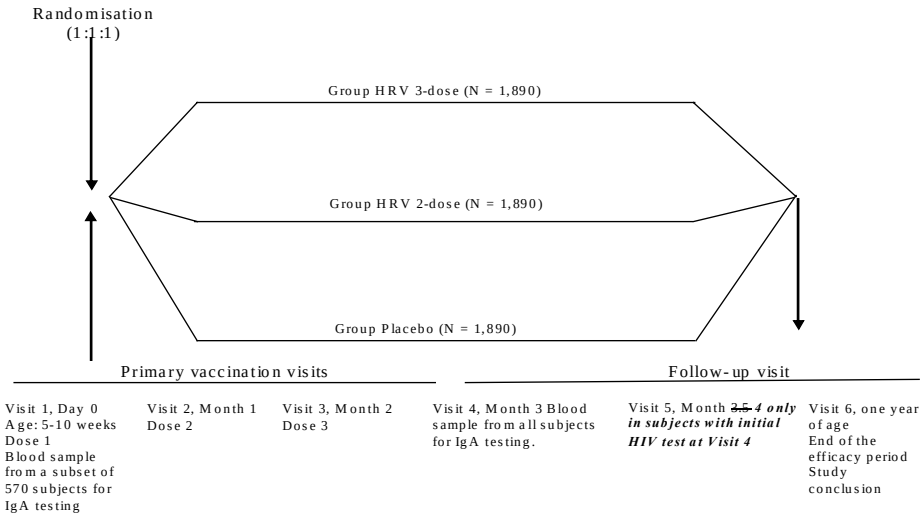
Study staff will visit the subject every week to check for occurrence of any diarrhoea during the entire study period.

- Results of HIV testing on blood samples collected ***after informed consent for HIV testing has been obtained*** will be communicated to the parents/guardians at ***the subsequent visit/contact***. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***at the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. If ***an initial*** ~~confirmatory~~ HIV test is done ***at Visit 4***, ~~the parents/guardians will have~~ ***there will be*** an additional study visit (Visit 5 ~~approximately 2 weeks~~ ***21-48 days*** after Visit 4) so that the study staff can inform ***parents/guardians of HIV test results*** and offer ~~further~~ ***post-test*** counselling. ***If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling.*** Results of the HIV test should be recorded in the CRF.
- In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] and Standard of Care provided during GSK sponsored trials.
- ~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found

to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed (due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

Section 3



Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Blood sample to be collected from all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample at the subsequent visit from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.

Synopsis (Number of subjects) and Section 4.1

No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1.

Blood sample ~~at Visit 3~~ from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***after the initial test*** ~~at Visit 3~~ and are asymptomatic.

Section 4.1

A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi. Enrolment will ***continue until a total of 5670 subjects are enrolled in the study*** ~~be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa and a minimum of 2670 subjects to be enrolled in Malawi~~

As of January 2006 a total of 1,827 subjects have been enrolled in South Africa (Cohort 1 in South Africa). Enrolment in South Africa was suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa shall resume after the RV season to enrol the total planned number of subjects (Cohort 2 in South Africa).

No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1.

Blood sample ~~at Visit 3~~ from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***after the initial test*** ~~at Visit 3~~ and are asymptomatic.

Section 4.2

- Written informed consent obtained from the parent or guardian of the subject ***who is of legal age (i.e. parent/guardian should be 18 years or older)***.
- ***In South Africa, birth weight > 2000 g or if weight unknown, gestation period > 36 weeks.***

Section 5.1.2

In addition to the Informed Consent Form at Visit 1 to participate in this study, parents/guardians will be presented with ***an informed consent form summary and a feedback form as well as*** a second Informed Consent Form to obtain consent for HIV testing of the subjects. ***The HIV test will be proposed and ideally performed at visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible.***

Section 5.2

Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa.

Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit ~~3~~ ***1.***

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Pre-test counselling and informed consent for HIV testing will be performed. A blood sample will be obtained from all subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on ***collected*** blood samples will be communicated to the parents/guardians at ***the subsequent visit/contact***. Post-test counselling will be offered to mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***after the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. Results of the HIV test should be recorded in the CRF. ~~If a confirmatory HIV test is done, the parents/guardians have to return for Visit 5 (approximately two weeks after Visit 4) so that the study staff can inform them of the HIV test results and offer further counselling.~~ ***.Subjects who undergo the initial HIV testing at Visit 4 will have an additional visit so that the study staff can inform parents/guardians of HIV test results and offer post-test counselling. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling***.

In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] and Standard of Care provided during GSK sponsored trials.

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ~~at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing ***will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If

the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed (due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

National Guidelines in South Africa recommend HIV testing ~~3 months~~ ***6 weeks*** after breast feeding cessation ~~which usually corresponds to 9 months old~~. ***This testing will be done through the usual clinic/paediatric outpatient system.*** The results of repeat test after breast feeding ceases ~~in HIV exposed subjects in South Africa who were negative at Visit 3~~ should be recorded in the CRF.

- GE surveillance:

  Study staff will visit the subject every week to check for the occurrences of any GE during the entire study period.

The study staff will direct the parents/guardians to the nearest hospital/medical facility ~~for~~ as necessary.

Section 5.4

Table 1 List of study procedures *for cohort 2 enrolled in South Africa and all subjects enrolled in Malawi*

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month ~~3~~ *4***	**1 year of age**
Sampling timepoint	**Pre**		**~~Post vacc 2~~**	**Post vacc 3**		
Informed consent addendum for HIV testing*†*	•		•	•		
Medical history for HIV	#•		•			
For HIV testing, ***if and when accepted‡***	***• (3 ml in South Africa and 1 ml in Malawi)***		~~• (3 ml in South Africa and 1 ml in Malawi) in subjects whose parent/ guardian has given consent at Visit 3~~	***• (3 ml in South Africa and 1 ml in Malawi)*** ~~• (2 ml in South Africa and 1 ml in Malawi) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test~~		
Confirmatory HIV testing, if required		***• (2 ml in South Africa and 1 ml in Malawi)***			***• (2 ml in South Africa and 1 ml in Malawi)***	

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month ~~3~~ *4***	**1 year of age**
Sampling timepoint	**Pre**		**~~Post vacc 2~~**	**Post vacc 3**		
Record results of HIV testing		•	•	•	•	
Inform subjects of HIV result		•	•	•	•	

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries ***(See Section 5.5 and Section 5.6.2).*** (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006)

†***Visit 5 will take place 21-48 days after Visit 4 o***nly in subjects ***who had an initial HIV test at Visit 4*** ~~needing a confirmatory HIV test~~

‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit.

†During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.

Table2 Intervals between study visits *for cohort 2 enrolled in South Africa and all subjects enrolled in Malawi*

Interval	**Size of interval**
4 (Visit 4→Visit 5)	***21*** ~~7~~ to 48 days

Refer to Annex 3 for list of study procedures and intervals between study visits for cohort 1 enrolled in South Africa.

Section 5.5

Cohort 1 enrolled in South Africa

Refer to Annex 3 for detailed description of study visits for cohort 1 enrolled in South Africa.

Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- ***Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.***
- ***Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent.***

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When materials are provided by GSK Biologicals or designated laboratory, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the HIV test at the subsequent visit in the CRF.***
- ***Only in subjects who test HIV positive at the initial test and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test.***

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the confirmatory HIV test at the subsequent visit/contact in the CRF.***
- ***Communicate HIV test result of the confirmatory HIV test to parents/guardians at the subsequent visit/contact and post-test counselling.***

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- ***Proposal for HIV testing to parents/guardians. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ***Record medical history with regards to HIV exposure in the CRF.***

Visit 2, Month 1, Dose 2 (28-48 days after Visit 1)

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling and collection of blood samples for confirmatory HIV test if required.***

Visit 3, Month 2, Dose 3 (28-48 days after Visit 2)

- ***If confirmatory HIV test done at the preceding visit, communicate the results of the HIV to parents/guardians, record results of HIV test in the CRF and post-test counselling.***
- ~~Record medical history with regards to HIV exposure in the CRF. (Amendment 1: 24 August 2005)~~
- ~~Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling. (Amendment 1: 24 August 2005)~~
- ~~Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals or designated laboratory, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E. (Amendment 1: 24 August 2005)~~

- ~~Record results of the HIV test at Visit 3 in the CRF. (Amendment 1: 24 August 2005)~~

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- ***Proposal for HIV testing to parents/guardians, if HIV testing not done previously. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ~~Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling. (Amendment 1: 24 August 2005).~~
- ~~Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.~~

- ~~Record results of the HIV test at Visit 4 in the CRF. (Amendment 1: 24 August 2005)~~

Visit 5, Month *4* ~~3.5,~~ Follow-up (~~7~~*21*- 48 days after Visit 4) Only for subjects who ~~needed confirmatory HIV testing~~ *had initial HIV test at Visit 4*

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling, collection of blood samples for confirmatory HIV test if required and planning for a contact to inform the parents/guardians about the confirmatory HIV test result in 2 weeks.***

Section 5.6.2

GE Stool analysis

All stool samples collected during diarrhoea episodes from Visit 1 to Visit 6 will be processed at the study site ***or designated laboratory*** and shipped frozen to GSK Biologicals, Belgium.

HIV assay

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

HIV testing ~~at Visit 3~~ will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at ***the initial test*** ~~Visit 3~~ and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit*** ~~Visit 4~~.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing ***will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

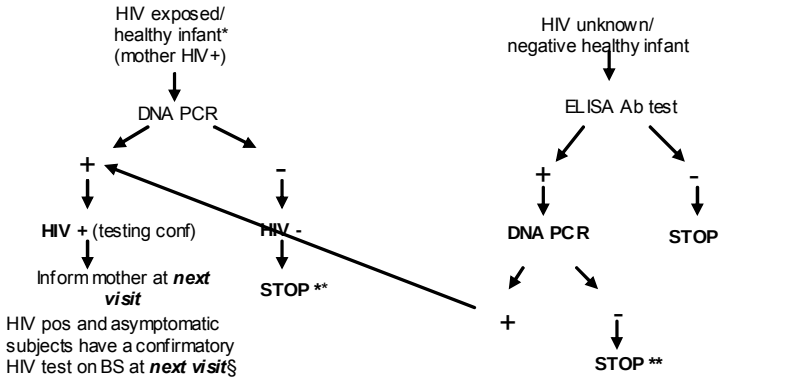
South Africa

HIV testing will be done according to the algorithm presented in Figure 1 (see below) based on the guidelines HIV testing guidelines in children from the Department of Health, South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] as outlined in Annex 2.

National Guidelines in South Africa recommend HIV testing ~~3 months~~ ***6 weeks*** after breast feeding cessation ~~which usually corresponds to 9 months old~~. ***This testing will be done through the usual clinic/paediatric outpatient system.*** The results of the repeat test after breast feeding ceases should be recorded in the CRF.

In case of discrepancy between HIV test results at ***initial and confirmatory tests*** ~~Visit 3 and Visit 4~~ (HIV positive at ***initial test*** ~~Visit 3~~, negative at ***confirmatory test*** ~~Visit 4~~), the HIV test should be repeated on the ***confirmatory test***~~Visit 4~~ blood sample If the discrepancy remains, the child should be sent to an ARV roll out center for HIV repeat test on a new blood sample according to National Guidelines in South Africa.

Figure 3 Algorithm for HIV testing in South Africa



* If infant has signs of HIV infection or has to be hospitalized ***(WHO interim stages III and IV) and any HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible***
** In South Africa: If breast-feeding : repeat test ***6 weeks*** after breast-feeding cessation
§ documented study contact ***for subjects with confirmatory HIV test***

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR ***at the initial HIV test*** ~~Visit 3~~ and asymptomatic	None

In South Africa, based on the result of the HIV assay, access to further testing, treatment or counselling will be available to subjects in South Africa as per the national guidelines in South Africa ***[South African National Department of Health Guidelines for the Management of HIV-infected Children 2005]*** (also refer to Section 5.2).

Section 6.2

Should the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered at that visit. The subject may continue to participate ~~to~~ ***in*** the study and will not be excluded from the planned analyses.

Section 6.4.1

To allow GSK Biologicals to take advantages of greater rates of recruitment than anticipated at individual centres in this multicenter study, and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

Section 6.4.3

No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1.

Section 6.5

A set of individual codes will be held at the ~~local GSK Biologicals' Safety Office and~~ GSK Biologicals' Central Safety Office. ~~If there is no local Safety Office, a set of individual codes will be held by the Medical Monitor.~~

Section 8

During the follow-up period from Visit 6 to Visit 7, serious adverse events (SAEs) and adverse events leading to drop-outs (AE*) will be recorded.

Section 8.4 and Section 8.7

~~If not yet performed, HIV testing will be encouraged at hospital admission, and the results should be recorded in the CRF. (Amendment 1: 24 August 2005)~~ ***During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.***

Section 8.12

In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] and Standard of Care provided during GSK sponsored trials.

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

Section 10.6.1

HIV status at Visit ~~3~~ ***1*** and Visit 4 will be presented.

Appendix A

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

Appendix C

- A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi. Enrolment will ***continue until a total of 5670 subjects are enrolled in the study*** ~~be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa and a minimum of 2670 subjects to be enrolled in Malawi~~.
- ***As of January 2006 a total of 1,827 subjects have been enrolled in South Africa (Cohort 1 in South Africa). Enrolment in South Africa was suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa shall resume after the RV season to enrol the total planned number of subjects (Cohort 2 in South Africa).***

Appendix D

3. Preparation of aliquot

- Stool samples collected during specified timepoints and gastroenteritis episodes will be processed, at the study site ***or designated laboratory***, to prepare an aliquot in a 8 ml tube.

Annex 2

Source: ~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***Guidelines for the Management of HIV-infected Children 2005***. Accessed on the website ~~http://www.doh.gov.za/search/index.html~~ ***http://www.doh.gov.za/docs/factsheets/guidelines/hiv/index.html.***

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102248 (Rota-037) & 111274 (ROTA-037 EXT:Y2)
Administrative Change 2

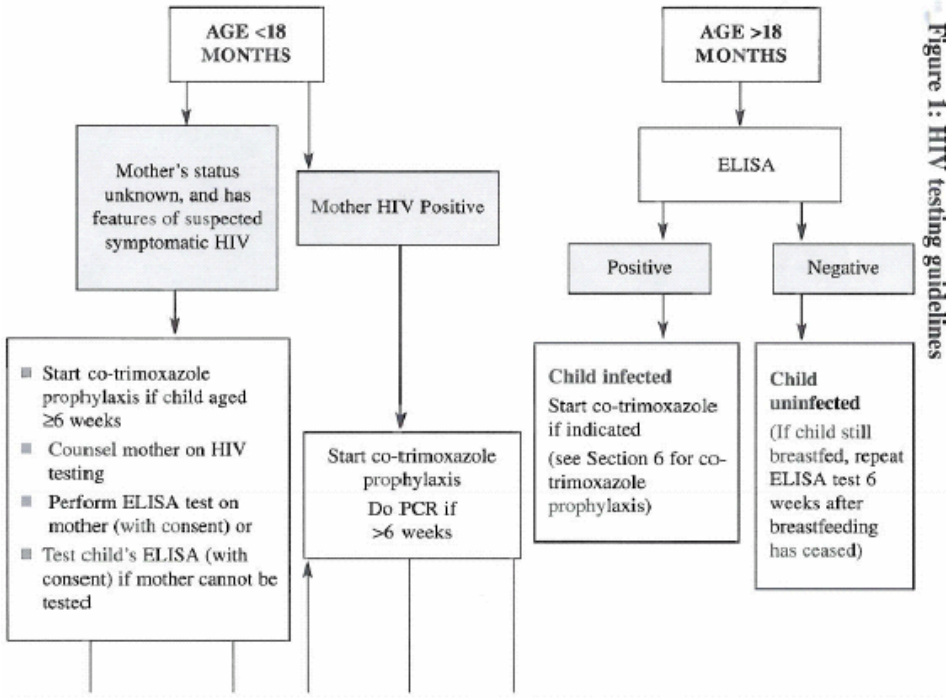
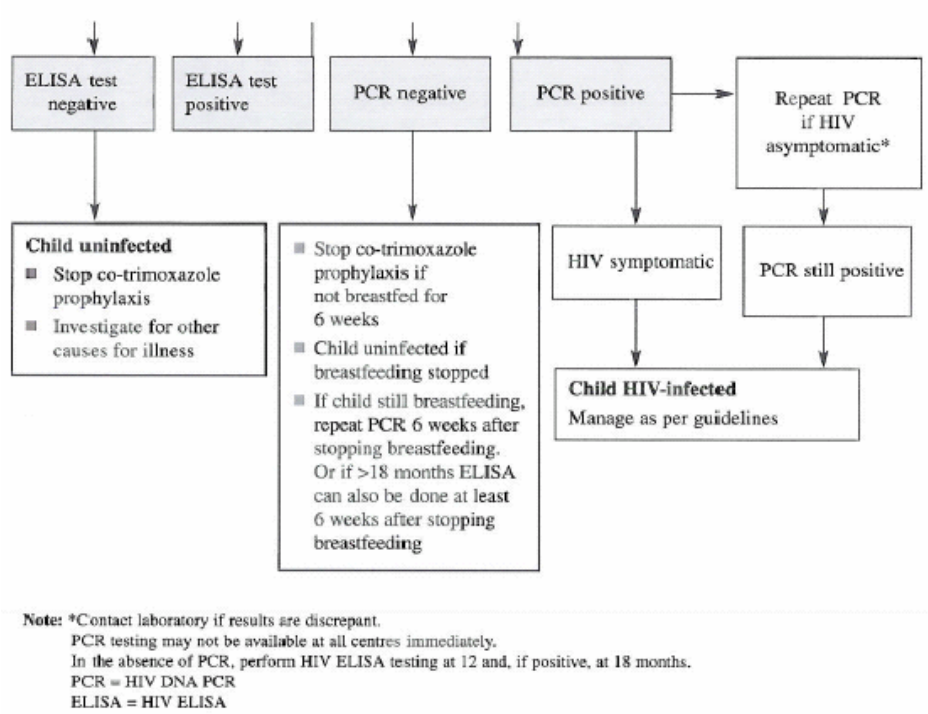


Figure 1: HIV testing guidelines



Note: *Contact laboratory if results are discrepant.
PCR testing may not be available at all centres immediately.
In the absence of PCR, perform HIV ELISA testing at 12 and, if positive, at 18 months.
PCR = HIV DNA PCR
ELISA = HIV ELISA

Annex 3

Annex 3 Study procedures for cohort 1 enrolled in South Africa as per Amendment 2 dated 27 October 2005 was added.

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	Rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Amendment 6
Amendment date:	**2 August 2007**
Co-ordinating authors:	[redacted] [redacted] Scientific Writers

Rationale/background for changes: This amendment was done on 2 August 2007 to implement the following changes for the South Africa cohort as recommended by the Rotavirus Vaccine Program (RVP) organization which co-sponsors this study.

- To perform an interim analysis on efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. This interim analysis is performed under the request by RVP to allow early review of African efficacy data to prepare implementation of universal mass vaccination (UMV) in some African countries. The availability of earlier results suggesting favourable efficacy of the vaccine in developing countries in Africa would be useful as an advocacy tool to stimulate policy makers both at global level (e.g. WHO, SAGE, GAVI) and at the country level to prepare for accelerated decision-making and introduction activities in Africa.
- To extend follow-up for efficacy until the end of the second consecutive RV season for Cohort 2 South Africa. Also, safety follow-up for SAEs and AEs leading to drop out will be performed for these subjects until the end of the RV season. The follow-up during the second year will also be performed for the cohort in Malawi. Additional follow-up may allow for the estimation of vaccine efficacy, either among all infants over the combined first and second year of life or during the second year of life. Additional follow-up may also provide greater power to investigate other aspects of vaccine efficacy such as protection among infants in these populations with high HIV prevelance, better estimation of strain and dose-specific vaccine efficacy.
- To implement a supplementary ICF to allow using post-breast feeding cessation HIV results in the analysis when HIV test is performed.

- To implement administrative changes to update the study team in GSK Biologicals, Rixensart.
- The sample size of the study population was adjusted as the actual number of RV GE episodes reported so far indicated that the initially planned incidence of 1.5% for severe RV GE cases in the placebo group during the first efficacy period was too conservative. Hence, the incidence rate was revised and a 2% incidence rate has been considered. Thus, the total number of subjects to be enrolled in the study has been decreased.

Amended text has been indicated in bold italics in the following sections:

Title page (Co-ordinating authors)

[redacted] Scientific Writer***s***

Title page (Contributing authors)

[redacted] Director

[redacted] Central Study Coordinator

[redacted] Clinical Development Manager

Sponsor signatory: [redacted] Director

List of Abbreviations

RVP Rotavirus Vaccine Program

Glossary of Terms

Efficacy follow-up period: ~~All subjects will be followed until one year of age~~ ***S***ubjects ***in Cohort 1 South Africa*** will be followed until one year of age. ***Subjects in Cohort 2 South Africa will continue efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).***

Synopsis (Definitions)

Efficacy follow-up period: ~~All~~ ***S***ubjects ***in Cohort 1 South Africa*** will be followed until one year of age. ***Subjects in Cohort 2 South Africa will continue efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).***

Synopsis (References)

Cunliffe NA, Kilgore PE, Bresee JS, et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. Bull World Health Organ. 1998;76:525-37.

De Zoysa I, Feachem RV. Intervention for the control of diarrheal disease among children: rotavirus and cholera immunization. Bull World Health Organ. 1985;63:569-83.

Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis. 1990; 22:259-67.

Steele AD, Peenze I, de Beer MC, et al. Anticipating rotavirus vaccines: epidemiology and surveillance of rotavirus in South Africa. Vaccine. 2003;21:354-60.

Synopsis (secondary objectives) and Section 2.2

For subjects in Cohort 2 South Africa and the cohort in Malawi:

- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE (≥11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7.***
- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***

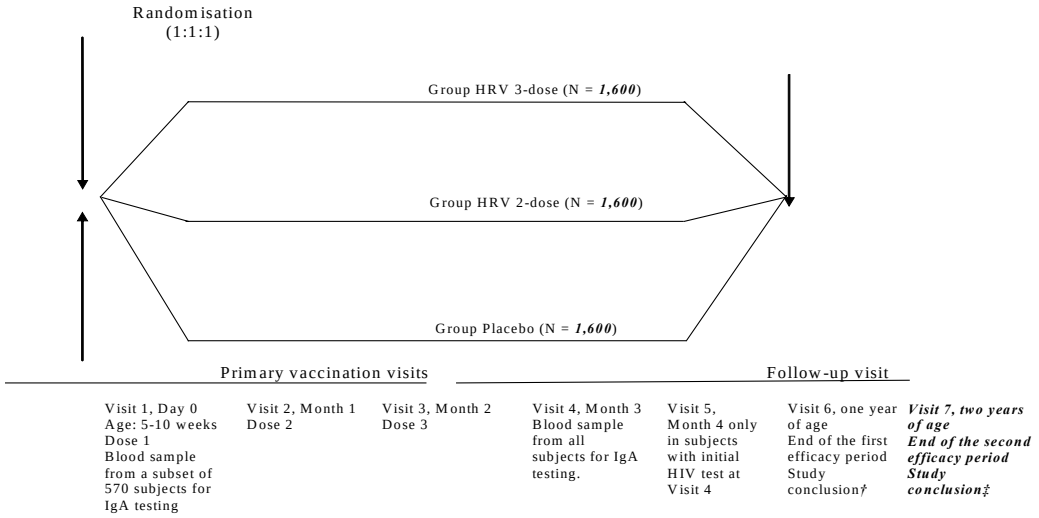
Section 1.1

Please refer to the latest version of the investigator brochure (Edition ~~5~~ ***8***) for a detailed review of other information on the HRV vaccine.

Section 1.2

Although this HRV vaccine is registered in Malawi and ***South Africa, and*** will become available in the private market; a placebo controlled trial is justified as the vaccine is not available through public health care programmes to the general population.

Section 3



† For subjects in Cohort 1 South Africa
‡ For subjects in Cohort 2 South Africa and the Cohort in Malawi

Synopsis (study design) and Section 3

- Treatment Groups:
  - Group HRV 3-Dose: 3 doses of HRV given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N = ~~1,890~~ ***1,600***)
  - Group HRV 2-Dose: 2 doses of HRV given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose will be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding) (N = ~~1,890~~ ***1,600***)
  - Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N = ~~1,890~~ ***1,600)***

For subjects in Cohort 2 South Africa, efficacy and safety follow-up will continue until the end of the RV season in 2008 (between 1 August 2008 and 15 September

2008). For all subjects in Malawi, efficacy and safety follow-up will continue until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). These subjects will have an additional visit i.e. Visit 7.

Visit 6 (at one year of age) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) ***for subjects in Cohort 1 and 2 in South Africa and the Cohort in Malawi*** and study conclusion ***for all the subjects in Cohort 1 South Africa. A supplementary ICF will be provided to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed. A supplementary ICF will be provided to the parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi to request their child's/ward's participation in the second year follow-up for this study.***

Visit 7, only for subjects in Cohort 2 South Africa (at the end of the RV season in 2008 i.e. between 1 August 2008 and 15 September 2008) and for all subjects in the Cohort in Malawi (until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) and study conclusion.

Results of HIV test conducted post-breast feeding cessation will be recorded in the CRF when consent to do so has been obtained from the subject's parents/guardians.

During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and*** from Visit 1 up until Visit ***7 for subjects in Cohort 2 South Africa***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed ***at the site*** or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa, HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics or hospitals, as indicated as per clinical symptoms.***HIV testing performed at hospital admission should be recorded in the CRF.

- Recording of height and weight at Visit 1, Visit 4, Visit 6 and ***Visit 7***.
- Active follow-up for occurrence of GE episodes (diarrhoea) via weekly visit to a subject by study personnel during the entire study period (from the day of Dose 1 until Visit 6 ***for subjects in Cohort 1 South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***)).
- ***Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period. Results of the analysis for efficacy and***

safety data collected during the second efficacy follow-up period will be provided in an annex report.

- ***An interim analysis on vaccine efficacy against severe RV GE and any RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind.***
- Duration of the study: The study subjects ***in Cohort 1 in South Africa*** will be followed until one year of age, ***and the*** intended duration of the study, per subject, will not exceed a maximum of 10 to 11 months. ***The study subjects in Cohort 2 South Africa will be followed until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008), and the intended duration of the study, per subject, will not exceed a maximum of 24 months. The study subjects in the Cohort in Malawi will be followed until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) and the study duration will not exceed a maximum of 24 months.***

Synopsis (number of subjects) and Section 4.1

~~A minimum of 2,600 subjects will be enrolled in South Africa and a maximum of 3070 subjects will be enrolled in Malawi.~~

~~Enrolment will be terminated when 4,800 subjects have been enrolled.~~

Total target enrolment will be ~~5,670~~ ***4,800*** subjects (~~1,890~~ ***1,600*** subjects in each group).

All enrolled subjects will be followed for efficacy and safety. The subjects in ***Cohort 1 in South Africa*** will be followed for efficacy and safety until one year of age. ***The subjects in Cohort 2 South Africa will be followed for efficacy and safety until the end of the 2008 RV season (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).***

Section 5.1.2

The parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi, who are interested to continue the participation of their child in the second year follow-up will be presented an ICF supplement to obtain their written informed consent.

An ICF will also be given to the parents/guardians of subjects (irrespective of their decision to let their child/ward participate in the second year follow-up period but for whom HIV test will be performed on the child/ward post cessation of breast feeding) to obtain their consent to record the results of HIV tests conducted post-breast feeding cessation in the CRF when performed.

Section 5.2

- During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 up until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the ***site*** or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.*** HIV testing performed at hospital admission should be recorded in the CRF.
- National Guidelines ***for the management of HIV infected children*** in South Africa recommend HIV testing 6 weeks after breast feeding cessation ***and the National Guidelines for the management of HIV infected children in Malawi recommends the HIV testing 3 months after breast feeding cessation.*** This testing will be done through the usual clinic/paediatric outpatient system. The results of repeat test after breast feeding ceases should be recorded in the CRF.
- ~~All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF. (Amendment 1: 24 August 2005).~~
- GE surveillance:

  Active surveillance for GE (diarrhoea) will be conducted by the study staff during the entire study period (starting at Dose 1 until Visit 6 ***for subjects in Cohort 1 in South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 in South Africa and the Cohort in Malawi***).

- Collection of stool samples:

  Parents/guardians of all subjects will be instructed to collect stool sample(s) if the subject develops diarrhoea at any time until Visit 6 ***for subjects in Cohort 1 in South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi.***

Section 5.4

Table 1 List of study procedures for Cohort 1 and 2 enrolled in South Africa and all subjects enrolled in Malawi

Age	**5-10 weeks**						
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**	***VISIT 7***
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**1 year of age**	***End of 2nd efficacy follow-up period***
Sampling timepoint	**Pre**			**Post vacc 3**			
Informed consent	•						
Informed consent addendum for HIV testing§	•			•			
Supplementary ICF for using results of HIV testing performed after breast feeding cessation						•	
Supplementary ICF for participation in 2nd efficacy follow-up						•	
Medical history	•						
Medical history for HIV	•						
Check of inclusion criteria	•						
Check of exclusion criteria	•						
Check of elimination criteria		•	•	•		•	•
Check of contraindications	•	•	•				
Randomisation	•						
Physical examination	•	#	#	#		#	#
Pre-vaccination body temperature	•	•	•				
Measure/record height and weight	•			•		•	•
Blood sampling							
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects			
For HIV testing, if and when accepted‡	• (3 ml in South Africa and 1 ml in Malawi)			• (3 ml in South Africa and 1 ml in Malawi)			
Confirmatory HIV testing, if required		• (2 ml in South Africa and 1 ml in Malawi)			• (2 ml in South Africa and 1 ml in Malawi)		
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•	•
Study vaccination (HRV or placebo)	•	•	•				
Routine EPI vaccination	•	•	•				
Recording of AEs leading to drop-out	•	•	•	•		•	•

Age	**5-10 weeks**						
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**	***VISIT 7***
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**1 year of age**	***End of 2nd efficacy follow-up period***
Sampling timepoint	**Pre**			**Post vacc 3**			
Return of completed diary cards by parents/guardians		•	•	•		•	•
Diary card transcription		•	•	•		•	•
Recording concomitant medication/vaccination	•	•	•	•		•**	•**
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•	•
Record results of HIV testing		•	•		•		
Inform subjects of HIV result		•	•		•		
Record results of HIV testing after breast feeding ceases						•	•
Study Conclusion						•	•

§During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the ***site*** or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.***

•** Only concomitant medication administered for treatment of GE, AE leading to drop-outs and SAEs will be recorded during this period.

Visit 7 is for subjects in Cohort 2 South Africa and the Cohort in Malawi only.

Table 2 Intervals between study visits for Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

Interval	**Size of interval**
Visit 7	***1 August 2008 - 15 September 2008 (end of RV season) for Cohort 2 South Africa and until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) for the Cohort in Malawi***

Section 5.5

Visit 6, Follow-up (343-391 days of age)

- ~~Study conclusion.~~
- Record any concomitant~~/intercurrent vaccinations and~~ medications administered ***for the treatment of GE, SAEs and AEs leading to drop-outs*** in the CRF.
- ***The parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi, who are interested to continue the participation of their child in the second year follow-up will be presented a supplementary ICF to obtain their written informed consent.***

- ***A supplementary ICF will be presented to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed.***
- ***A 'GE diary card' will be provided to parents/guardians of all subjects who provide consent to continue participation during the second efficacy follow-up period, and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 7. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.***
- ***Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.***
- ***Parents/guardians should contact the study physician or study staff if the subject manifests any of these signs or symptoms and that they perceive as serious.***
- ***Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.***

Visit 7, Follow-up (end of RV season 2008 i.e. between 1 August 2008 and 15 September 2008 for subjects in Cohort 2 South Africa and until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009 for all subjects in Malawi)
Visit 7 is for subjects in Cohort 2 South Africa and the Cohort in Malawi only.

- ***Physical examination.***
- ***Recording of height and weight.***
- ***Check of elimination criteria.***
- ***Record any concomitant medications administered for the treatment of GE, SAEs and AEs leading to drop-outs in the CRF.***
- ***Recording of SAEs that may have occurred since Visit 6.***
- ***Record results of HIV testing after breast feeding cessation in the CRF if consent to use the results was obtained from the parents/guardiand and if the HIV test was perfomed since the previous visit.***
- ***Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.***
- ***Return any stool samples.***
- ***Record AEs leading to drop-out in the CRF.***
- ***Study conclusion.***

Section 5.6.2

All stool samples collected during diarrhoea episodes from Visit 1 to Visit ~~6~~ ***7*** will be processed at the study site or designated laboratory and shipped frozen to GSK Biologicals, Belgium.

HIV assay

- During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi*****),** if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing and the concerned informed consent will be proposed at the site, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.***

Figure 1 Algorithm for HIV testing in South Africa

Note: DNA testing using PCR as specified in the Figure 1 is applicable to subjects only up to 18 months of age, whose mothers tested positive for HIV or for whom their mother's status was not known but the ELISA was reactive. ELISA tests would be performed on subjects after 18 months of age. As per the South African Guidelines no DNA PCRs will be performed for subjects after 18 months of age.

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times from Visit 1 until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***			RV antigen	All	None

Section 6.4

Target enrolment will be ~~5,670~~ ***4,800*** subjects (~~1,890~~ ***1,600*** subjects in each group).

Section 6.5

Blinding will be maintained for the whole study period (see Section 10.7 for details on how the individual blinding will be maintained despite statistical analyses before all study data are collected/processed). This will allow unbiased evaluation of the study vaccine.

Section 6.9

Concomitant medication administered for the treatment of a ***SAE and AE**** within the follow-up period for adverse events must be recorded in the CRF 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.

Any investigational medication or vaccine administered throughout the study (from Visit 1 to Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***) must be recorded in the CRF.

Any ARV therapy given throughout the study (from Visit 1 to Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***) must be recorded in the CRF.

Section 8.4

During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi)*** ~~must be recorded in the CRF~~)), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.*** HIV testing performed at hospital admission should be recorded in the CRF.

Section 8.5

All AEs leading to subject withdrawal/drop-out during the period starting at Visit 1 and ending at Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi*** must be recorded in the subject's CRF.

Section 8.6.1

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for AEs leading to drop-out ~~from Visit 1 to Visit 6~~ and SAEs reported from Visit 1 to Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***.

Section 8.7

During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed ***at the site*** or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.***

Section 8.8.2

Study Contact for Reporting SAEs
Refer to the Sponsor Information Sheet
Back-up Study Contact for Reporting SAEs Refer to the Sponsor Information Sheet
GSK Biologicals Clinical Safety Physician Tel: [redacted] Fax: [redacted] [redacted]
Mobile phone for 7/7 day availability: [redacted] (Head Safety Evaluation and Risk Management Paediatrics) Back-up mobile phone contact: [redacted]
24/24 hour and 7/7 day availability

Section 8.12

Treatment of any adverse event ***leading to drop-outs and SAEs*** is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE* and ***SAEs*** should be recorded in the subject's CRF.

Synopsis (secondary endpoints) and Section 10.2

For subjects in Cohort 2 South Africa:

- ***Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***

Section 10.3

A total of ~~5,670~~ ***4,800*** subjects (~~1,890~~ ***1,600*** subjects in each group) will be enrolled. Allowing for approximately 15% of subjects who may not be evaluable for analyses of

the primary objective, ~~4,800~~ ***3,960*** evaluable subjects (~~1,600~~ ***1,320*** subjects in each group) are expected to be evaluable for the analysis of the primary objective.

Assuming a ***2%*** incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of ~~4,800~~ ***3,960*** evaluable subjects has ~~80%~~ ***84%*** power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).

~~**Table 5 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,600 evaluable subjects, N HRV pooled groups = 3,200 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)**~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6~~		
	~~60%~~	~~70%~~	~~80%~~
~~1%~~	~~60%~~	~~78%~~	~~92%~~
~~1.5%*~~	~~80%~~	~~93%~~	~~98%~~
~~2%~~	~~90%~~	~~98%~~	~~99%~~
~~3 %~~	~~98%~~	~~99%~~	~~100%~~

~~*Anticipated incidence rate~~

Table 5 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = *1,320* evaluable subjects, N HRV pooled groups = *2,640* evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6		
	60%*	70%	80%
1%	***50%***	***69%***	***86%***
1.5%	***71%***	***87%***	***97%***
2%*	***84%***	***95%***	***99%***
3 %	***95%***	***99%***	***99%***

*Anticipated incidence rate

~~**Table 6 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,600 evaluable subjects, N HRV group = 1,600 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)**~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6~~		
	~~60%~~	~~70%~~	~~80%~~
~~1%~~	~~46%~~	~~64%~~	~~82%~~
~~1.5%*~~	~~66%~~	~~84%~~	~~95%~~
~~2%~~	~~80%~~	~~93%~~	~~98%~~
~~3 %~~	~~93%~~	~~99%~~	~~99%~~

~~*Anticipated incidence rate~~

Table 6 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,320 evaluable subjects, N HRV group = 1,320 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6*		
	60%	*70%*	*80%*
1%	*38%*	*55%*	*73%*
1.5%	*57%*	*76%*	*90%*
*2%**	*71%*	*88%*	*97%*
3 %	*89%*	*97%*	*99%*

Anticipated incidence rate

Estimation of power for the second efficacy period

With respect to the year 2 efficacy follow-up, Table 7 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy. If the VE is truly 60% and assuming a 2% incidence of severe RV GE in the placebo group, a sample size of 2325 evaluable subjects has 59% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95% CI on vaccine efficacy >0%).

Table 7 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 775 evaluable subjects, N HRV pooled groups = 1550 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from Visit 6 up to Visit 7*		
	*60%**	*70%*	*80%*
1%	29%	43%	60%
*2%**	59%	78%	92%
3 %	79%	93%	99%

****Anticipated incidence rate***

Section 10.4

Total vaccinated cohort

- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects ~~for whom efficacy follow-up data are available after dose 1 of HRV vaccine or placebo~~.

According-to-protocol (ATP) safety cohort

- who have not received a replacement vial, ***except if the appropriate vaccine was administered in "double-blind replacement"***.

ATP efficacy cohort

- who have entered into the efficacy surveillance period:
  - have follow-up beyond 2 weeks after the last dose of the study vaccination course ***for analysis of the first and combined efficacy follow-up periods.***
  - ***have*** follow***-up beyond the end of the first efficacy follow-up period for analysis of the second efficacy follow-up period.***

Section 10.6

Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. (Amendment 1: 24 August 2005). ***A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period***.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed after subjects have completed Visit 7, and will be presented in an annex report.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 6. However, access to the individual treatment

decode will be provided to the investigators only after the final analyses of the second efficacy follow-up has been performed.

Section 10.6.2

In addition, vaccine efficacy will be calculated, with their 95% CI, against

- ***severe RV GE caused by the circulating wild-type RV strains, hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE, severe RV GE (G1 and non-G1) for the second and combined efficacy periods and for pooled HRV groups.***
- ***severe RV GE caused by the circulating wild-type RV strains after 3 doses of HRV vaccine versus 2 doses of HRV vaccine for the combined efficacy period.***

Section 10.6.3

The height and weight increase from Visit 1 to Visits 4, 6 and *7* will be summarised by group.

Section 10.7

~~There is no planned interim analysis~~.

An interim analysis on vaccine efficacy against severe RV GE and any RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be descriptive and will not be used to conclude on vaccine efficacy.The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. The interim analysis will be based on the total vaccinated cohort for the subset of subjects with efficacy follow-up 2 weeks beyond study dose 3. The estimated VE against any wild-type RV GE and severe wild-type RV GE will be provided for the pooled HRV groups versus the placebo group. Distribution of RV GE by serotype will also be available although this will not be provided by group.The interim analysis will be dissemintated within GSK and shared with the RVP organization and the investigators.

Table 8 indicates the level of accuracy that can be expected for the interim evaluation of efficacy against severe RV GE.

Table 8 Power at interim analysis to get an exact confidence interval for the vaccine efficacy above 0% for a true VE of 60% and 70%, and for different total number of severe RV GE episodes reported (ratio 2:1 (pooled HRV groups:placebo), alpha=0.1%, PASS 2005)

Total number of severe RV GE episodes reported in the three groups	*Power*	
	Vaccine efficacy of 60%	*Vaccine efficacy of 70%*
80	*81%*	*98%*
70	*71%*	*96%*
65	*65%*	*94%*
60	*58%*	*90%*
40	*34%*	*70%*
30	*25%*	*54%*
20	*14%*	*32%*
10	*2%*	*6%*

Since the interim analysis will be descriptive and will not be used to conclude on vaccine efficacy, no adjustment on the alpha will be applied for the final analyses of efficacy.

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Appendix C

- Target enrolment will be ~~5,670~~ ***4,800*** eligible subjects.
- ~~Enrolment will continue until a total of ***4,800*** subjects are enrolled in the study. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006).~~
- ~~Recruitment will be terminated when 5,670 eligible subjects have been enrolled.~~
- ~~A minimum of 2,600 subjects will be enrolled in South Africa and a maximum of 3070 subjects will be enrolled in Malawi.~~ Enrolment will continue until a total of ~~5670~~ ***4,800*** subjects are enrolled in the study.
- The intended duration of the study ***for subjects in Cohort 1 South Africa***, per subject, will not exceed a maximum of 10 to 11 months. ***The intended duration of the study, per subject, will not exceed a maximum of 24 months for subjects in Cohort 2 South Africa and the Cohort in Malawi.***

GlaxoSmithKline Biologicals	
Clinical Research & Development	
Protocol Administrative Change Approval	
eTrack study number *and abbreviated title*	102248 (Rota-037)
	111274 (ROTA-037 EXT:Y2)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Administrative Change number:	**Administrative Change 2**
Administrative Change date:	**30 August 2007**
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: This administrative change was done on 30 August 2007 to implement an eTrack number for the second follow-up period in this study. A few changes were made to align with the v12.5 of the GSK Standard Protocol Document Standard.	

Amended text has been indicated in bold italics in the following sections:

Title page

eTrack study number *and abbreviated title*	102248 (Rota-037)
	111274 (ROTA-037 EXT:Y2)

Date of ~~approval~~ *protocol*

The sponsor signature page and the investigator signature page were moved to the front of the document.

Protocol Administrative Change Sponsor Signatory Approval

Protocol Administrative Change Investigator Agreement

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-track #
Rota-037 (South Africa)	102248

Date: 30 March 2009

***Concerns:* Missing Protocol Approval Pages**

Details:

There will be no signed protocol approval pages in the ROTA-037 files for Dr.[redacted] as she was designated national PI for regulatory reasons but was not responsible for one particular site.

GSM Responsible:[redacted]

Signature:[redacted]

Signature Date: 30 MAR 2009

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-track #
Rota-037 (South Africa)	102248

Date: 02 April 2009
Concerns: Signature pages for Dr.[redacted] and Dr.[redacted]

Details:

This file notes is intended to clarify some misunderstandings of previous file notes dated 29 May 2008 and 26 Mar 2008.

Administrative change 1 was made to the protocol on 22 September 2005. This change did not warrant a signature from the Investigators however, Dr.[redacted] did sign this administrative change.

Protocol amendment #2 on 27 October 2005 allowing participation of a second country, Malawi, added country specific changes to the protocol and administrative updates were made. This change did not affect doctors[redacted] and[redacted] since they are in South Africa and Investigators participating in South Africa were not asked to sign for this. Although a signature was not required Dr[redacted] signed the amendment.

Dr.[redacted] signed Amendment #5 when it was not needed as he did not participate in cohort 2.

There were no signatures for Amendment #6 and administrative change for Drs.[redacted] and[redacted] as both had stopped their participation at this point in time.

GSM Responsible:[redacted]

Signature[redacted]

Signature Date: April 2nd 09

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102248
Final

eTrack study number	102248
eTrack abbreviated title	rota-037
Date of approval	27 April 2005
Title	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants in South Africa.

Sponsor signatory approval

Sponsor signatory: [redacted] Associate Director

Signature: [redacted]

Date: [redacted] 27 APR 2005

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- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

21 OCT 2005

Investigator signature **Date**

Rota -037
Centers [redacted]

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Investigator name: Dr [redacted]

[redacted]

Invest[redacted]ature

2005/10/26
Date

Rota 037
Chrer [redacted]

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Investigator name: DR. [redacted]

[redacted] 17/OCT/2005

Investigator signature [redacted] **Date**

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Center [redacted]

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Investigator name: [redacted]

[redacted]

12/10/05

Investigator sig[redacted] **Date**

Rota-037
Center [redacted]

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Investigator name: Dr [redacted]

[redacted]

Investigator signature

01/11/05

Date

Rota-037
Center [redacted]

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Final

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Investigator name: [redacted]

[redacted]

Investigator signature

17/10/2005

Date

Rota_037
Center [redacted]

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Final

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Investigator name: Dr [redacted]

[redacted]
Investigator signature

13/10/2005.
Date

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Investigator name: [redacted]

Investigator signature [redacted] 12 Oct 2005

Date

Rota-037
Centre [redacted]

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted]

Investigator signature

17 OCT 2005

Date

Rota-037
Center [redacted]

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- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted]

[redacted]

Investig[redacted] signature

14.10.05

Date

Rota-037
Centre [redacted]

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- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: Dr [redacted]

[redacted] 18 Oct 2005

Investigator signature **Date**

Rota-037
Center [redacted]

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**
Amendment number:	Amendment 1
Amendment date:	24 August 2005
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes:

This protocol was amended on 24 August 2005 to implement the following changes:

- To increase the sample size: The assumed attack rate of 2% for severe RV GE for sample size estimation in the original protocol was found to be too optimistic based on the results obtained in several studies with GSK Biologicals' HRV vaccine. A more conservative attack rate of 1.5% was therefore considered and the sample size was revised.
- In the context of the increased sample size, to specify the target enrolment in South Africa.
- To allow HIV testing according to the national guidelines in south Africa. HIV testing will be perfomed at Visit 3 in all subjects whose parents/guardians gave consent, followed by a confirmatory test at Visit 4 in HIV positive subjects who are asymptomatic.
- To add an additional study visit to communicate results of the confirmatory HIV test to the parents/guradians.
- To change method of data collection from Remote Data Entry to Case Report Forms.
- Following feedback from the ERCs, changes to reflect local clnical practice for care and treatment were made.

Amended text has been included in *bold italics* in the following sections. Deleted text is shown in strikethrough below.

Cover page

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[redacted] ~~Associate~~ Director

Study title
A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants ~~in South Africa~~.

List of abbreviations

CRF	***Case Report Form***
~~**eCRF**~~	~~**Electronic Case Report Form**~~

Glossary of terms

Rotavirus (RV) GE ***caused by the circulating wild-type rotavirus strain*:**	
RV season ***in South Africa*:**	Based on epidemiological observations in South Africa, the RV season will be considered during the period from March 01 to ~~June 30~~ ***July 31.***

Section 1.1
~~Based on the year 2000 HIV prevalence estimate of 22.9% (95% C.I. 20.1; 25.7%) for adults in the Northwest Province where study rota-014 was conducted and with transmission of HIV from mother to child reported from 20 to 70% in South Africa we estimated that there were about 20 infants who were HIV positive.~~

The 2004 annual antenatal survey indicated that HIV prevalence among pregnant women is 29.5% (CI 28.5% - 30.5%) compared to the 27.9% (CI 26.8% - 28.9%) observed in 2003 [Department of Health, South Africa***,*** 2004***].***

Synopsis (Rationale) and Section 1.2
Continuing evaluation of the HRV vaccine in Africa, this study will evaluate the efficacy, safety and immunogenicity of the HRV vaccine at the selected optimum virus concentration in healthy ~~South~~ African infants when given concomitantly with routine Expanded Program of Immunisation (EPI) vaccines.

- To determine if the GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*. **(Amendment 1: 24 August 2005)**.

Criteria: The primary objective will be reached if the lower limit of the of the 95% CI on vaccine efficacy is >0%.

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Refer to Section 10.1 for definition of the primary endpoint.

Synopsis (Primary Objective) and Section 2.1

- To determine if the GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations can prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.

Synopsis (Secondary Objectives) and Section 2.2
Efficacy

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.
- To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the of HRV vaccine or placebo until Visit ~~5~~*6*.
- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last

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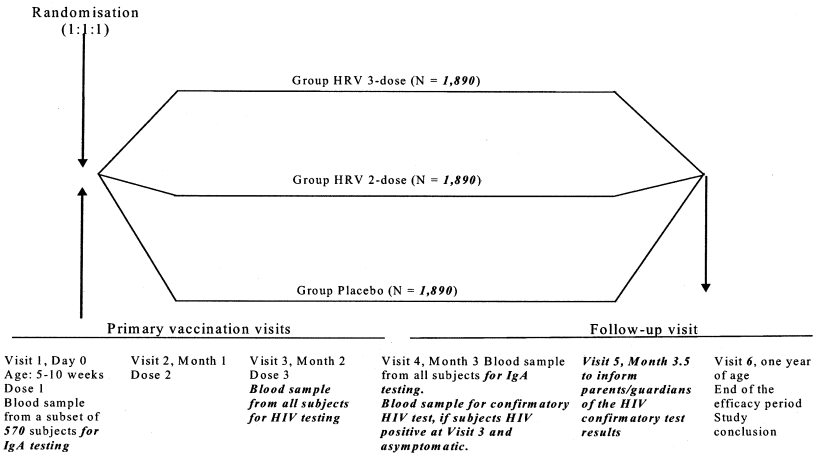
dose of HRV vaccine or placebo until Visit ~~5~~*6* for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season.

- To assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups and for each HRV group) given concomitantly with routine EPI vaccinations to prevent severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~*6*.

Section 3



Synopsis (Study design) and Section 3

- Group HRV 3-Dose: 3 doses of HRV given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N=~~1,410~~ *1,890*)
- Group HRV 2-Dose: 2 doses of HRV given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose will be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding) (N=~~1,410~~ *1,890*)
- Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N=~~1,410~~ *1,890*)

- All subjects will have five study visits ***(Visit 1, 2, 3, 4 and 6). Subjects who undergo HIV testing at Visit 4 will have one additional visit (Visit 5):***

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=~~420~~*570*), Dose 1 of HRV vaccine or placebo and routine EPI vaccines.

  Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.***

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Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive at Visit 3 and are asymptomatic for a confirmatory HIV test.***

Visit 5 (Month 3.5) Only in Subjects with confirmatory HIV testing at Visit 4 – Inform parents/guardians of the confirmatory HIV test's results and offer further counselling.

Visit ~~5~~ ***6*** (at one year of age) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) and study conclusion.

- Routine EPI schedule vaccinations (~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) should be administered concomitantly with the study vaccine at Visit 1, 2 and 3 following the EPI recommendation (at approximately 6, 10 and 14 weeks of age) and documented in the CRF.
- Recording of height and weight at Visit 1, Visit 4 and Visit ~~5~~***6***.
- Blood samples will be collected from a subset of subjects (N=~~420~~***570*** subjects) at Visit 1 and from all subjects at Visit 4 ***to measure anti-rotavirus IgA antibodies.***

  Blood sample at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at Visit 4 from subjects who test HIV positive at Visit 3 and are asymptomatic.
- Active follow-up for occurrence of GE episodes (diarrhoea) via weekly visit to a subject by study personnel during the entire study period (from the day of Dose 1 until Visit ~~5~~***6***).
- ***Results of HIV testing on blood samples collected at Visit 3 will be communicated to the parents/guardians at Visit 4.*** Pre-test ***and post-test*** counselling will be offered to all mothers or guardians of study subjects ***who consented for HIV testing*** ~~at the centers. Counselling will be offered to mothers or guardians of HIV-positive subjects at the centers.~~ ***For subjects who test HIV positive at Visit 3 and are asymptomatic, a confirmatory HIV test should be performed at Visit 4. If a confirmatory HIV test is done, the parents/guardians will have to visit the study site approximately two weeks after Visit 4 (Contact 1) so that the study staff can inform them of the confirmatory HIV test results and offer further counselling. Results of the HIV test should be recorded in the CRF.***

  In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [***National Antiretroviral Treatment Guidelines, First Edition, 2004***] and Standard of Care provided during GSK sponsored trials.

Synopsis (Study design), Abbreviations, Sections 3, 4.3, 5.1.1, 5.2, 5.4, 5.5, 6.2, 6.4.2, 6.6, 6.9, 8.1, 8.4, 8.5, 8.6.1, 8.12, 9.2.1 and 9.2.2.
References to "Remote Data Entry (RDE) and Electronic Case Report Form (eCRF)" replaced with "Case Report Form (CRF)".

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Final

Synopsis (Number of subjects)
Total target enrolment will be ***5,670 subjects*** (***1,890 subjects in each group*** ~~4,230 subjects (1,410 subjects in each group~~).

A subset of ~~420~~***570*** subjects will provide a blood sample at Visit 1 and all subjects will provide a blood sample at Visit 4 ***to measure anti-rotavirus IgA antibodies***.

Blood sample at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at Visit 4 from subjects who test HIV positive at Visit 3 and are asymptomatic.

Section 4.1
Total target enrolment will be ***5,670 subjects*** (***1,890 subjects in each group*** ~~4,230 subjects (1,410 subjects in each group~~).

All subjects will be enrolled at multiple sites in ~~South~~ Africa.

A minimum of 2,600 subjects will be enrolled in South Africa. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa.

Enrolment will be terminated when ~~4,230~~ ***5,670*** subjects have been enrolled.

A subset of ~~420~~***570*** subjects will provide a blood sample at Visit 1 ***to measure anti-rotavirus IgA antibodies***. All subjects will provide a blood sample at Visit 4 to assess the immunogenicity of study vaccines ***(anti-rotavirus IgA antibodies)***.

Blood sample at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at Visit 4 from subjects who test HIV positive at Visit 3 and are asymptomatic.

Section 5.1.
When the World Medical Association amended the Declaration in October 2000, GSK, other pharmaceutical companies and other stakeholders who sponsor studies did not accept the literal interpretations of the revised paragraphs 29 and 30. In the case of paragraph 29, we consider that there are situations in which there is a scientific need for a placebo control and in these particular circumstances, this is not intrinsically unethical. Additionally, this aspect of study design will in any case be reviewed by the relevant Ethics Committee.

In the case of paragraph 30, that statement assumed - without reference to the overall stage of development of the experimental product - that the results of individual studies could justify the continued treatment of study subjects with the experimental product and indeed, oblige sponsors to provide it irrespective of the state of knowledge at that time and of many other important practical issues eg availability of supplies.

These are the reasons for GSK referencing the 1996 version of the Declaration of Helsinki. In the case of this particular study, the changes introduced in 2000 by paragraphs 29 and 30 are not relevant to the design or conduct of this study.

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Section 5.1.2

In addition to the Informed Consent Form at Visit 1 to participate in this study, parents/guardians will be presented with a second Informed Consent Form at Visit 3 to obtain consent for HIV testing of the subjects.

Section 5.2

- ***Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit 3.***
- ***Pre-test counselling and informed consent for HIV testing will be performed at Visit 3. A blood sample will be obtained at Visit 3 from all subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on blood samples collected at Visit 3 will be communicated to the parents/guardians at Visit 4. Post-test*** counselling will be offered to mothers or guardians ***of study subjects who consented for HIV testing. For subjects who test HIV positive at Visit 3 and are asymptomatic, a confirmatory HIV test should be performed at Visit 4. If a confirmatory HIV test is done, the parents/guardians will have an additional study visit (Visit 5 approximately 2 weeks after Visit 4) so that the study staff can inform them of the confirmatory HIV test results and offer further counselling. Results of the HIV test should be recorded in the CRF.***

  In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [***National Antiretroviral Treatment Guidelines, First Edition, 2004***] and Standard of Care provided during GSK sponsored trials. GSK Biologicals will facilitate access to ARV treatment centers for any children who test HIV positive at Visit 3, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

- ***If a child develops symptoms indicative of AIDS (WHO stages II or III), or has to be hospitalised before Visit 3, HIV testing and the concerned Informed Consent will be proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatoryHIV test will be performed as necessary.***
- ***National Guidelines in South Africa recommend HIV testing 3 months after breast feeding cessation which usually corresponds to 9 month old. The results of repeat test after breast feeding ceases should be recorded in the CRF.***
- ***As part of the clinical practice at the study site, mothers together with their infants who are HIV positive will be offered support and facilitated access to ARV treatment centers where they will receive prophylaxis and care.***
- ***As part of the clinical practice at the study site, infants who have diarrhoea should be offered care and treatment at the study site during the study.***
- Active surveillance for GE (diarrhoea) will be conducted by the study staff during the entire study period (starting at Dose 1 until Visit ~~5~~*6*).
- Parents/guardians of all subjects will be instructed to collect stool sample(s) if the subject develops diarrhoea at any time until Visit ~~5~~*6*.

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Section 5.4

Age	5-10 weeks					
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	*VISIT 5†*	VISIT ~~5~~*6*
Timing	Day 0	Month 1	Month 2	Month 3	Month 3.5	1 year of age
Sampling timepoint	Pre		*Post vacc 2*	Post vacc 3		
Informed consent addendum for HIV testing			•			
Medical history for HIV	#		•			
Blood sampling						
To test anti-rotavirus IgA antibodies	•* (2 ml) in subset (N=570)			• (2 ml) in all subjects		
For HIV testing			*• (3 ml) in subjects whose parent/ guardian has given consent at Visit 3*	*• (2 ml) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test*		
Record results of HIV testing			•	•		
Inform subjects of HIV result				•	•	
Record results of HIV testing after breast feeding ceases						•

†Only in subjects with confirmatory HIV test

• is used to indicate a study procedure which requires documentation in the individual CRF.

is used to indicate a study procedure which does not require documentation in the individual CRF.

Table 2 Intervals between study visits

Interval	Size of interval
4 (Visit 4→Visit 5)	*7 to 48 days*
Visit ~~5~~*6*	343-391 days of age

Section 5.5

Visit 1, Day 0: 5-10 weeks of age, Dose 1

– Administration of Dose 1 of the routine EPI vaccine (~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) in all groups.

Visit 2, Month 1, Dose 2 (30-48 days after Visit 1)

– Administration of Dose 2 of the routine EPI vaccine (~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) in all groups.

Visit 3, Month 2, Dose 3 (30-48 days after Visit 2)

- ***Record medical history with regards to HIV exposure in the CRF.***

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- ***Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.***
- ***Collection of 3 ml of whole blood for HIV testing from subjects whose parents/guardians gave consent.***

When materials are provided by GSK Biologicals or designated laboratory, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the HIV test at Visit 3 in the CRF.***
- Vaccination:
  - Administration of Dose 3 of the routine EPI vaccine ~~DTPw-HBV-Hib~~ ***DTPw-HB/Hib*** and OPV) in all groups.

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- ***Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling.***
- Collection of a blood sample for serology from all subjects: a minimum of ~~3~~*2* ml of whole blood to provide a minimum of ~~1.5~~*0.8* ml of serum according to instructions in Appendix D.
- ***Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of 2 ml of whole blood for a confirmatory HIV test.***
- ***Record results of the HIV test at Visit 4 in the CRF.***
- A 'GE diary card' will be provided to parents/guardians of all subjects and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit ~~5~~*6*.

Visit 5, Month 3.5, Follow-up (7- 48 days after Visit 4) Only for subjects who needed confirmatory HIV testing

- ***Communicate HIV test result from Visit 4 to parents/guardians and post-test counselling.***

Visit ~~5~~ *6*, Follow-up (343-391 days of age)

- Recording of SAEs that may have occurred since ***visit 4***
- ***Record results in the CRF if the HIV test was repeated after breast feeding cessation.***

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Section 5.6.2

GE Stool analysis

All stool samples collected during diarrhoea episodes from Visit 1 to Visit ~~5~~ ***6*** will be processed at the study site and shipped frozen to GSK Biologicals, Belgium. If any G1 RV is detected in the stool specimens, vaccine virus ~~will~~ ***may*** be differentiated from the wild type serotype by sequence analysis or an equivalent approach.

Serum analysis

Blood samples collected from a subset of ~~420~~***570*** subjects at Visit 1 and from all subjects at Visit 4 will be centrifuged and the separated serum should be stored at –20°C until shipped to GSK Biologicals, Belgium for analysis.

HIV assay

HIV testing will be done according to the algorithm presented in Figure 1 (see below) based on the guidelines HIV testing guidelines in children from the Department of Health, South Africa [National Antiretroviral Treatment Guidelines, First Edition, 2004] as outlined in Annex 2.

HIV testing at Visit 3 will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at Visit 3 and are asymptomatic, a confirmatory HIV test should be performed at Visit 4.

If a child develops symptoms indicative of AIDS (WHO stages II or III), or has to be hospitalised before Visit 3, HIV testing and the concerned Informed Consent will be proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.

National Guidelines in South Africa recommend HIV testing 3 months after breast feeding cessation which usually corresponds to 9 month old. The results of the repeat test after breast feeding ceases in HIV exposed subjects who were negative at visit 3 should be recorded in the CRF.

In case of discrepancy between HIV test results at Visit 3 and Visit 4 (HIV positive at Visit 3, negative at Visit 4), the HIV test should be repeated on the Visit 4 blood sample If the discrepancy remains, the child should be sent to an ARV roll out center for HIV repeat test on a new blood sample according to National Guidelines in South Africa.

HIV tests will be performed locally at designated laboratories accredited for HIV testing and using approved test kits (see last updated version of laboratory workbook for details of blood sample collection, transportation and testing) ~~(see laboratory workbook)~~.

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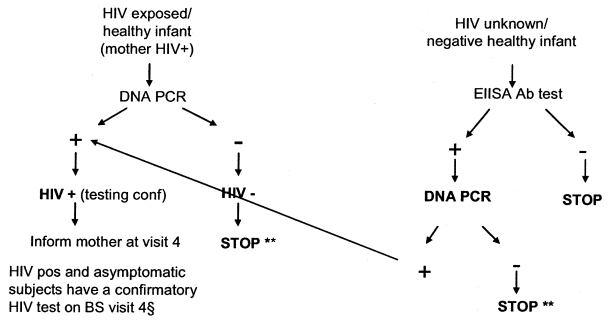
Figure 2 HIV testing algorithm



* If infant has signs of HIV infection or has to be hospitalized, his HIV status will be done before visit 3
** If breast-feeding : repeat test at 3 months after breast-feeding cessation
§ documented study contact after visit 4

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
GE stool analysis					
At all times from Visit 1 until Visit ~~5~~***6***			RV antigen	All	None
Serum analysis					
Timing	**Month**	**Visit no**			
Pre	Day 0	1	IgA anti-HRV	Subset of ***570*** subjects	None
Post-vacc 3	Month 3	4	IgA anti-HRV	All	None
HIV assay in *subjects whose parent/guardian gave consent*					
Post-vacc 2	***Month 2***	***3***	***Serum*** HIV antibody test ***(ELISA)***	***Subjects not exposed to HIV or HIV status unknown***	None
Post-vacc 2	***Month 2***	***3***	***Whole blood DNA PCR***	***- Subjects not exposed to HIV and positive for HIV antibody*** ***- Subjects exposed to HIV***	None
Post-vacc 3	***Month 3***	***4***	***Whole blood DNA PCR***	***Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic***	***None***

Any additional testing on biological samples to further evaluate the immunogenicity of the ***HRV*** vaccine ***(such as neutralisation assay)*** will be performed if deemed necessary by GSK Biologicals if any findings in the present study necessitate further investigation of the vaccine.

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Based on the result of the HIV assay, access to further testing, treatment or counselling will be available ***to subjects in South Africa*** as per the national guidelines in South Africa (also refer to Section 5.2).

Section 6.4
Target enrolment will be ~~4,230 subjects (1,410 subjects in each group)~~ ***5,670 subjects (1,890 subjects in each group)***.

Section 6.4.3
The subset of ~~420~~***570*** subjects (~~140~~ ***190*** subjects per group) from selected sites will provide a blood sample at Visit 1.

Section 6.9
Any investigational medication or vaccine administered throughout the study (from Visit 1 to Visit ~~5~~***6***) must be recorded in the CRF.

Any ARV therapy given throughout the study (from Visit 1 to Visit 6) must be recorded in the CRF.

Section 8.5
All AEs leading to subject withdrawal/drop-out during the period starting at Visit 1 and ending at Visit ~~5~~ ***6*** must be recorded in the subject's CRF.

Section 8.6.1
The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for AEs leading to drop-out from Visit 1 to Visit ~~5~~ ***6*** and SAEs reported from Visit 1 to Visit ~~5~~ ***6***. The assessment will be based on the investigator's clinical judgement.

Section 8.11
Informtion on behavioral symptoms (determined as either normal, less playful/irritable, or lethargic/listless, or seizure) and their duration will be also recorded on the GE diary cards. This additional information will allow exploratory analysis of alternative scoring systems.

Section 8.12
In south Africa, procedures to be followed for ARV therapy will be in compliance with national guidelines in South Africa [Operational plan for comprehensive HIV and AIDS Care, Management and Treatment for South Africa 19 Nov 2003] and Standard of Care provided during GSK sponsored trials. GSK Biologicals will facilitate access to ARV treatment centers for any children who test HIV positive ~~at Visit 4~~, but decisions towards treatment will be taken by appropriate staff at these treatment centers. Pre-test ***and post-test*** counselling will be offered to all mothers or guardians of study subjects ***who consented for HIV testing***. ~~Counselling will be offered to mothers or guardians of HIV positive subjects at the centers.~~

Synopsis (Primary Endpoint) and Section 10.1

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains in pooled HRV

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groups versus the placebo group during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

Synopsis (Secondary Endpoints) and Section 10.2
Efficacy

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit ~~5~~ ***6***.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6*** for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

Section 10.3
~~A total of 4,230 subjects (1,410 subjects in each group) will be enrolled. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 3,600 evaluable subjects (1,200 subjects in each group) are expected to be evaluable for the analysis of the primary objective.~~

~~Considering a 1:1:1 randomisation ratio and various incidence rates expected in the study, Table 5 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy.~~

~~Assuming a 2% incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of 3,600 evaluable subjects has 80% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).~~

~~**Table 7 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,200 evaluable subjects, N HRV pooled groups = 2,400 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2**~~

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~~**groups, one-sided Chi-square test with continuity correction and arcsine transformation)**~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 5~~			
	~~60%~~	~~70%~~	~~80%~~	~~90%~~
~~1%~~	~~46%~~	~~65%~~	~~82%~~	~~95%~~
~~2%*~~	~~80%~~	~~94%~~	~~99%~~	~~100%~~
~~3 %~~	~~94%~~	~~99%~~	~~100%~~	~~100%~~

~~*Anticipated incidence rate (reference: Study rota-013)~~

~~Table 6 presents the power to detect a statistically significant difference between each HRV group and placebo group for a range of vaccine efficacy.~~

~~**Table 8 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,200 evaluable subjects, N HRV group = 1,200 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)**~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 5~~			
	~~60%~~	~~70%~~	~~80%~~	~~90%~~
~~1%~~	~~34%~~	~~50%~~	~~68%~~	~~86%~~
~~2%*~~	~~67%~~	~~84%~~	~~95%~~	~~100%~~
~~3 %~~	~~85%~~	~~96%~~	~~100%~~	~~100%~~

~~*Anticipated incidence rate (reference: Study rota-013)~~

A total of 5,670 subjects (1,890 subjects in each group) will be enrolled. Allowing for up to 15% of subjects who may not be evaluable for analyses of the primary objective, 4,800 evaluable subjects (1,600 subjects in each group) are expected to be evaluable for the analysis of the primary objective.

Considering a 1:1:1 randomisation ratio and various incidence rates expected in the study, Table 5 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy.

Assuming a 1.5% incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of 4,800 evaluable subjects has 80% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).

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Table 9 ***Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,600 evaluable subjects, N HRV pooled groups = 3,200 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)***

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6*		
	60%	*70%*	*80%*
1%	*60%*	*78%*	*92%*
*1.5%**	*80%*	*93%*	*98%*
2%	*90%*	*98%*	*99%*
3 %	*98%*	*99%*	*100%*

**Anticipated incidence rate*

Table 6 presents the power to detect a statistically significant difference between each HRV group and placebo group for a range of vaccine efficacy.

Table 10 ***Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,600 evaluable subjects, N HRV group = 1,600 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)***

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6*		
	60%	*70%*	*80%*
1%	*46%*	*64%*	*82%*
*1.5%**	*66%*	*84%*	*95%*
2%	*80%*	*93%*	*98%*
3 %	*93%*	*99%*	*99%*

**Anticipated incidence rate*

Section 10.6
Final analysis for efficacy, safety and immunogenicity will be performed when subjects have completed Visit ~~5~~ ***6*** at the end of the efficacy follow-up period.

Section 10.6.1
HIV ~~seropositivy~~ status at ***Visit 3 and*** Visit 4 will be presented.

Section 10.6.2
- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains

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during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

- Severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the HRV vaccine or placebo until Visit ~~5~~ ***6***.
- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6*** for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6***.

The primary objective will be reached if the lower limit of the 95%CI on vaccine efficacy for pooled HRV groups against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit ~~5~~ ***6*** is >0%.

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE requiring hospitalization, efficacy from Dose 1 until 2 weeks after Dose 2 of study vaccination, time to events analysis, ***efficacy against severe RV GE using alternative scoring systems other than the Vesikari system***).

Section 10.6.3
Exploratory safety analyses will be performed according to the HIV seropositivy status ~~at Visit 4~~.

The height and weight increase from Visit 1 to Visits 4 ***and 6*** will be summarised by group.

Appendix B
Instructions for Remote Data Entry replaced with Instructions for Case Report Form.

Appendix C
- The study will be conducted at multiple sites in ~~South~~ Africa.
- Target enrolment will be ~~4,230~~ ***5,670*** eligible subjects.
- Recruitment will be terminated when ~~4,230~~ ***5,670*** eligible subjects have been enrolled.

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- ***A minimum of 2,600 subjects will be enrolled in South Africa. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa.***

Appendix G

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 ***and including 5% over-randomisation.***

- ~~7,050~~ ***9,930*** doses of the HRV vaccine in monodose vials.
- ~~5,640~~ ***7,944*** doses of the placebo for HRV vaccine in monodose vials.
- ~~12,690~~ ***17,874*** doses of the diluent (calcium carbonate buffer) pre-filled syringes.

Sufficient doses of GSK Biologicals' OPV ***and DTPw-HB/Hib vaccines*** will be also provided to administer 3 doses of routine vaccines.

Annex 2

Annex 2 outlining the HIV testing guidelines in children was added.

[redacted]

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**
Amendment number:	Amendment 1
Amendment date:	24 August 2005
Approved by: Director	[redacted] 29-08-2005 dd-mm-yyyy

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GlaxoSmithKline Biologicals
Clinical Research & Development
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Amendment number:	Amendment 1
Amendment date:	24 August 2005
Agreed by:	[redacted]
Investigator:	
Investigator signature:	
Date:	6 JUL 06

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Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	24 August 2005

Agreed by:
Investigator: Dr [redacted]

Investigator signature: [redacted]

Date: 2006/01/10

13-JAN-2006 09:49 From [redacted] To [redacted] P.2/2

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Agreed by:	
Investigator:	
Investigator signature:	[redacted]
Date:	12/Jan/2006

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Amendment number:	Amendment 1
Amendment date:	24 August 2005
Agreed by: **Investigator:**	DR. [redacted]
Investigator signature:	
Date:	11.01.06

DR. [redacted] 17/01/06.

DR [redacted] 17/01/06

[redacted]

24.JAN.2006 15:39 NO.394 P.3

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Amendment date:	24 August 2005
Agreed by: **Investigator:** Dr	[redacted]
Investigator signature:	[redacted]
Date:	09/01/06

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Amendment number:	Amendment 1
Amendment date:	24 August 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] [redacted] 20/22 JAN/2006

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Amendment date:	24 August 2005
Agreed by:	
Investigator:	
Investigator signature:	[redacted]
Date:	24 Jan 2006

[redacted]

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GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**
Amendment number:	Amendment 1
Amendment date:	24 August 2005
Agreed by:	
Investigator:	[redacted]
Investigator signature:	
Date:	24 Jan 2006

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Amendment number:	Amendment 1
Amendment date:	24 August 2005
Agreed by:	
Investigator:	
Investigator signature:	[redacted]
Date:	12 JAN 2006

Dr. [redacted]

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Clinical Research & Development
Protocol Amendment Approval

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Amendment number:	Amendment 1
Amendment date:	24 August 2005
Agreed by:	
Investigator:	
Investigator signature:	[redacted]
Date:	17 JAN 2006

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Co-ordinating author:	[redacted] Scientific Writer

Rationale/background for changes: The following administrative changes were made to the protocol on 22 September 2005 as per the request of the WHO ERC:

- Declaration of Helsinki version 2004 will be used for this study instead of the 1996 version
- A summary of the Informed Consent will be used for better comprehension of the informed consent .
- A questionnaire will be used to monitor parent's/guardian's comprehension of the informed consent.

Amended text has been indicated in bold italics in the following sections:

Section 5.1

The study will be conducted according to Good Clinical Practice (GCP), the ~~1996~~ ***2004*** Declaration of Helsinki (Protocol Appendix A) and local rules and regulations of the country.

~~***When the World Medical Association amended the Declaration in October 2000, GSK, other pharmaceutical companies and other stakeholders who sponsor studies did not accept the literal interpretations of the revised paragraphs 29 and 30. In the case of paragraph 29, we consider that there are situations in which there is a scientific need for a placebo control and in these particular circumstances, this is not intrinsically unethical. Additionally, this aspect of study design will in any case be reviewed by the relevant Ethics Committee.***~~

~~***In the case of paragraph 30, that statement assumed - without reference to the overall stage of development of the experimental product - that the results of individual studies***~~

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~~***could justify the continued treatment of study subjects with the experimental product and indeed, oblige sponsors to provide it irrespective of the state of knowledge at that time and of many other important practical issues eg availability of supplies.***~~

~~***These are the reasons for GSK referencing the 1996 version of the Declaration of Helsinki. In the case of this particular study, the changes introduced in 2000 by paragraphs 29 and 30 are not relevant to the design or conduct of this study.***~~

Section 5.1.2
In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the ~~1996~~ ***2004*** Declaration of Helsinki.

An investigator or designate will describe the protocol to potential subjects' parents/guardians face to face. ***At the request of the [redacted], potential subjects' parents/guardians will receive a summary document with the gist of the Informed Consent Form to aid comprehension.***

At the request of the [redacted], all parents/guardians will have to complete an Informed Consent Feedback Form. The responses of the parents/guardians to the questions in the Informed Consent Feedback Form will allow the person taking informed consent to understand what has or has not been understood by the subjects' parents/guardians. In case of incorrect responses, the informed consent will be explained again to the parents/guardians and the investigator or his delegate will assess comprehension. Responses from parents/guardians of the first 50 subjects will be transmitted to the [redacted].

Appendix A
The 1996 Declaration of Helsinki was replaced with the 2004 Declaration of Helsinki.

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Approved by: Sponsor Signatory title	[redacted] 15th October 2005 dd-mm-yyyy

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-Track #
Rota – 037 (South Africa)	102248

Date: 29 May 2008

Concerns: Investigator Signature for Protocol Administrative Change 1 dated 22 September 2005

Details:

Background

The protocol was amended on 22 September 2005 to change the following sections in the protocol: Section 5.1 and section 5.1.2: The study will be conducted according to Good Clinical Practice (GCP), the ~~1996~~ **2004** Declaration of Helsinki (Protocol Appendix A) and local rules and regulations of the country.

Oversight

Investigators participating in South Africa were not asked to sign for this administrative change even though it was submitted to local regulatory authorities as well as all the ethics committees. Reason for this oversight could be related to the roles and responsibilities overlapping between the investigator, the SMO given the task to communicate with investigators and GSK local office.

Corrective Action:

File note for cohort 1 sites only as investigators are no longer actively involved in this trial. The investigators and sites are as follows:

[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]

Retrospective notification to investigators that are still actively participating/can still be contacted as well as retrospective signatures will be collected and filed. The investigators and sites are as follows:

[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]
[redacted] site [redacted] – Dr [redacted]

LSM Responsible : [redacted] **Signature Date: 29 May 2008**

[redacted]

~~CSC~~ GSM **Responsible :** [redacted] **Signature Date:** 29 MAY 2008

[redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Agreed by:	
Investigator:	
Investigator signature:	[redacted]
Date:	5 JUL 07

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GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Administrative Change Approval

Trial study number	102248
Trial abbreviated title	rota-037
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Administrative change number	Administrative change 1
Administrative change date	22 September 2005
Agreed by: (Investigator)	[redacted]
Investigator signature:	
Date:	29 MAY 2008

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:** 29/May/2008	[redacted]

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Agreed by:	
Investigator:	
Investigator signature:	[redacted]
Date:	29/05/08

[redacted] [redacted]

29 May 2008 16:19 p.2

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Agreed by: **Investigator:**	[redacted]
Investigator signature:	[redacted]
Date:	01/02/07.

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005

Agreed by:
Investigator: Dr [redacted]

Investigator signature: [redacted]

Date: 29/05/2008

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Agreed by: (Investigator)	[redacted]
Investigator signature:	[redacted]
Date:	29.5.08

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Administrative change number:	Administrative change 1
Administrative change date:	22 September 2005
Agreed by: **Investigator:** Dr [redacted]	
Investigator signature: [redacted]	
Date: 22 Sep 2007	

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: The protocol was amended on 27 October 2005 to allow participation of a second country, Malawi, in this study. Following addition of Malawi, some country-specific changes were made. Some administrative sections were updated.	

Amended text has been indicated in bold italics in the following sections:

Cover page

[redacted]***Clinical Development Manager***

Investor Agreement

- That I am thoroughly familiar with the appropriate use of the vaccine, as described in this protocol, and any other information provided by the sponsor, including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), ***and*** prescribing information (in the case of a marketed vaccine) ~~and/or Master Data Sheet (if the Master Data Sheet exists and serves as reference document for the vaccine in the case of a marketed vaccine)~~.

Glossary of terms

RV season in Malawi:	***The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. (Amendment 2: 27 October 2005)***

Synopsis (Secondary Objectives), Section 2.2

- ***In South Africa,*** to assess the efficacy of GSK Biologicals' HRV vaccine (for pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe

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RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (2 weeks post HRV dose 2 or 3) before the start of the RV season.

Synopsis (Definitions)

- RV season ***in South Africa***: Based on epidemiological observations, the RV season will be considered during the period from March 01 to June 30 in South Africa.
- ***RV season in Malawi: The impact of RV season in Malawi is minimal. While there can be a season defined, there are RV cases all year round. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year.***

Synopsis (Study design), Section 3

- Experimental design: Double-blind, randomised, placebo- controlled, multi-center, ***multi-country*** study with three parallel groups.

  In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] and Standard of Care provided during GSK sponsored trials.

Section 1.1

In South Africa, the disease was shown to be seasonal with a clear peak in autumn winter season [Steele , 2003]. ***In Malawi, RV is responsible for a third of outpatient attendances and hospital admissions for acute GE among children under 5 years of age [Cunliffe, 2001]. More than 80% of RV GE cases occur in infants less than one year of age. In Malawi, RV is identified throughout the year; diarrhoeal disease of all causes is most common during the warm, rainy season (November-March), but the proportion of diarrhoeal episodes attributed to RV is greatest during the cooler, dry season (May-September) [Cunliffe 2001 thesis]. The impact of RV season in Malawi is minimal. In terms of conduct of a clinical efficacy study it is thought that such a study can start at any given time in the year. Recently, the greater diversity of RV serotypes in some African countries has been recognized. In particular, serotypes G8 and P[6] have been documented in multiple settings, and in Malawi serotype G8 has comprised approximately 30% of all RV serotypes [Cunliffe, 1999; Cunliffe, 2001].***

As of ~~31 October 2004~~ ***15 July 2005***, the safety database for GSK Biologicals' HRV vaccine contains ~~80,383~~ ***89,243*** subjects. Up to ~~31 October 2004~~***15 July 2005***, ~~3,937~~ ***5,782*** subjects have reported a total of ~~4,525~~ ***6,872*** SAEs. Of these, a total of ~~59~~ ***67*** SAEs have been considered as possibly related by the investigators or with unknown relationship.

Section 4.1 and Appendix C

A minimum of 2,600 subjects will be enrolled in South Africa ***and 3070 subjects will be enrolled in Malawi***. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa ***and a minimum of 2670 subjects to be enrolled in Malawi***.

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Section 4.2

- Birth weight > 2000 g ***or if weight unknown, gestation period > 36 weeks.***

Section 5.2

- ***In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] and Standard of Care provided during GSK sponsored trials.***
- National Guidelines in South Africa recommend HIV testing 3 months after breast feeding cessation which usually corresponds to 9 month old. The results of repeat test after breast feeding ceases in HIV exposed subjects ***in South Africa*** who were negative at Visit 3 should be recorded in the CRF.

Section 5.4

Table 1 List of study procedures

Age	5-10 weeks					
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6
Timing	Day 0	Month 1	Month 2	Month 3	Month 3.5	1 year of age
Sampling timepoint	Pre		Post vacc 2	Post vacc 3		
To test anti-rotavirus IgA antibodies	•* (2 ml *in South Africa and 1 ml in Malawi*) in subset (N=570)			• (2 ml *in South Africa and 1 ml in Malawi*) in all subjects		
For HIV testing			• (3 ml *in South Africa and 1 ml in Malawi*) in subjects whose parent/ guardian has given consent at Visit 3	• (2 ml *in South Africa and 1 ml in Malawi*) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test		

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries

Table 2 Intervals between study visits

Interval	Size of interval
1 (Visit 1→Visit 2)	~~30~~ *28* to 48 days
2 (Visit 2→Visit 3)	~~30~~*28* to 48 days

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Section 5.5

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- Collection of pre-vaccination blood sample for serology from a subset of 570 subjects:
  - ***In South Africa,*** a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.
  - ***In Malawi, a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.***

Visit 2, Month 1, Dose 2 (~~30~~ *28*-48 days after Visit 1)

Visit 3, Month 2, Dose 3 (~~30~~ *28*-48 days after Visit 2)

- Collection of whole blood *(*~~of~~ 3 ml ***in South Africa and 1 ml in Malawi)*** for HIV testing from subjects whose parents/guardians gave consent.

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- Collection of a blood sample for serology from all subjects:
  - ***In South Africa,*** a minimum of 2 ml of whole blood to provide a minimum of 0.8 ml of serum according to instructions in Appendix D.
  - ***In Malawi, a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.***
- Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood *(*2 ml ***in South Africa and 1 ml in Malawi)*** for a confirmatory HIV test.

Section 5.6.1

Back-ups of stool samples will be maintained (see Appendix D) and should be used only for additional shipments in case mailed samples are lost.

Section 5.6.2

HIV assay

South Africa

Figure 1 Algorithm for HIV testing in South Africa

** *In South Africa*: If breast-feeding : repeat test at 3 months after breast-feeding cessation

Malawi

For all subjects whose parents gave consent for HIV testing, HIV status will be determined by employing 2 commercially available rapid HIV antibody tests, currently in use by the Malawi's HIV-testing program (Determine and Unigold). Discrepant HIV

results will be verified by PCR testing. When rapid HIV antibody test results are positive, PCR testing will be done. Subjects who test HIV positive at Visit 3 and are asymptomatic will undergo PCR testing at Visit 4.

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	Month	Visit no			
GE stool analysis					
At all times from Visit 1 until Visit 6			RV antigen	All	None
Serum analysis					
Timing	Month	Visit no			
Pre	Day 0	1	IgA anti-HRV	Subset of 570 subjects	None
Post-vacc 3	Month 3	4	IgA anti-HRV	All	None
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
Post-vacc 2	Month 2	3	Serum HIV antibody test (ELISA)	Subjects not exposed to HIV or HIV status unknown	None
Post-vacc 2	Month 2	3	Whole blood DNA PCR	- Subjects not exposed to HIV and positive for HIV antibody - Subjects exposed to HIV	None
Post-vacc 3	Month 3	4	Whole blood DNA PCR	Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic	None
Malawi					
Post-vacc 2	*Month 2*	*3*	*rapid HIV antibody tests*	*All*	*None*
Post-vacc 2	*Month 2*	*3*	*Whole blood DNA PCR*	*Subjects positive by rapid HIV antibody tests or in case of discrepancy*	*None*
Post-vacc 3	*Month 3*	*4*	*Whole blood DNA PCR*	*Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic*	*None*

In South Africa, based on the result of the HIV assay, access to further testing, treatment or counselling will be available to subjects in South Africa as per the national guidelines in South Africa (also refer to Section 5.2).

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] (also refer to Section 5.2).

Section 8.8.2

The Study Contacts per country (where available) are provided as a separate protocol attachment (refer to Attachment 1); in the case where the Study Contact is not available, you must contact the back-up Study Contact (see below).

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~~Study Contact for Reporting SAEs~~
~~Dr~~ [redacted] ~~Tel~~ [redacted] ~~Cell:~~ [redacted] ~~Fax:~~ [redacted] [redacted] ~~Tel:~~ [redacted] ~~Cell:~~ [redacted] ~~Fax~~ [redacted]

Section 8.12

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi draft February 2003] and Standard of Care provided during GSK sponsored trials.

Synopsis (Secondary endpoints), Section 10.2

- ***In South Africa,*** occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.

Section 10.6.2

- ***In South Africa, s***evere RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.

Appendix D

Instructions for Handling of Stool Samples

3. Preparation of aliquot

- ***After the aliquot to be shipped to GSK Biologicals' is prepared, a back-up sample should be maintained using excess material.***

4. Sorting and storage

- ***The back-up sample should be stored at a temperature between -20°C and -70°C at least until arrival of the shipped sample at GSK Biologicals, Rixensart has been confirmed.***

Appendix G

1. Vaccine and/or other supplies

In South Africa, sufficient doses of GSK Biologicals' OPV and DTPw-HB/Hib vaccines will be also provided to administer 3 doses of routine vaccines. ***In Malawi, local EPI vaccinations (OPV and DTPw-HB/Hib) will be used.***

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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Approved by: Sponsor Signatory title [redacted]	30 Nov 2005 dd-mm-yyyy

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-Track #
Rota – 037 (South Africa)	102248

Date: 26 March 2008

Concerns: Investigator Signature for Amendment 2 dated 27 October 2005

Details:

Background

The protocol was amended on 27 October 2005 to allow participation of a second country, Malawi, in this study and following addition of Malawi, some country specific changes were made and some administrative sections were updated.

Oversight

Investigators participating in South Africa were not asked to sign for this amendment as it had no practical implications for them.

MCC and ethics committees were however notified of these changes.

Corrective Action:

File note for cohort 1 sites only as investigators are no longer actively involved in this trial. The investigators and sites are as follows:

[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]

Retrospective notification to investigators that are still actively participating as well as retrospective signatures will be collected and filed. The investigators and sites

are as follows:

[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]
[redacted] – Dr [redacted]

LSM Responsible : [redacted]

[redacted]

Signature Date: 26 March 2008

CSC Responsible :

[redacted]

Signature Date: 26 MAR 2008

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
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Agreed by: Investigator: Investigator signature:	[redacted]
Date:	31 MARCH 07

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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Agreed by: **Investigator:** Dr [redacted]	
Investigator signature: [redacted]	
Date: 17 APR 2008	

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
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Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Agreed by: **Investigator:** **Investigator signature:** **Date:** 27 JUNE 2006	[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change Approval**	
eTrack study number	102248
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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Agreed by: **Investigator:** Dr [redacted] **Investigator signature:** [redacted] **Date:** 15/02/07	

GlaxoSmithKline Biologicals
Clinical Research & Development
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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Agreed by:	
Investigator:	[redacted]
Investigator signature:	[redacted]
Date:	07 Jul 2006 [redacted]

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Administrative Change Approval

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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005

Agreed by:
Investigator: Dr [redacted]

Investigator signature: [redacted]

Date: 01 Sep 2008

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Administrative Change Approval

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Administrative change number:	Amendment 2
Administrative change date:	27 October 2005
Agreed by: [redacted] **Investigator:** [redacted] **Investigator signature:** [redacted] **Date:** 24th April 2006	

102248(rota-037)
CONFIDENTIAL Final

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
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Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Malawi-specific Amendment 3
Amendment date:	**22 February 2006**
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: The protocol was amended on **22 February 2006** to implement specific changes for Malawi following ERC review.	

Amended text has been indicated in bold italics in the following sections:

Section 1.1

A recent review estimates that 611,000 (range 454,000–705,000) RV-related deaths occur in children under 5 years of age annually [Parashar, 2006]. From 2000 to 2004, RV was estimated to cause 39% of hospitalizations for childhood diarrhea. ~~It is 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 a total of 440,000-452,000 deaths in children under 5 years of age annually [Parashar , 2003]~~.

Synopsis (Rationale) and Section 1.2

Although this HRV vaccine is registered in Malawi and will become available in the private market; a placebo controlled trial is justified as the vaccine is not available through public health care programmes to the general population. More importantly as the vaccine is not yet recommended in the National Immunisation Guidelines, the data generated in this trial might facilitate evidence-based decisions on population-based vaccine utilisation in the country in particular and the region in general.

Section 4.2

- ~~Birth weight > 2000 g *or* ***if weight unknown, gestation period > 36 weeks.*** **(Amendment 2: 27 October 2005)**~~

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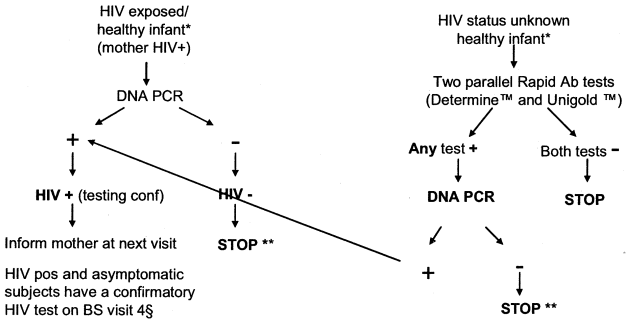
CONFIDENTIAL Final

Section 3, Section 5.2, Section 5.6.2 and Section 8.12

In Malawi, procedures to be followed for ARV therapy will be in compliance with national guidelines [National AIDS commission of Malawi, and, Ministry of Health and Population, Malawi Treatment of AIDS. Guidelines for the use of antiretroviral therapy in Malawi ~~draft February 2003~~*(1st edition October 2003 or later edition)*] and Standard of Care provided during GSK sponsored trials.

Figure 4 Algorithm for HIV testing in Malawi



* If infant has signs of HIV infection or has to be hospitalized, his HIV status will be done before visit 3
** If breast-feeding : repeat test at 3 months after breast-feeding cessation.
§ documented study contact after visit 4

Section 5.6.2

When ***any of the two*** rapid HIV antibody test results are positive, PCR testing will be done.

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
HIV assay in subjects whose parent/guardian gave consent					
Malawi					
Post-vacc 2	Month 2	3	Whole blood DNA PCR	Subjects positive by ***any of the two*** rapid HIV antibody tests or in case of discrepancy	None

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Final

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Clinical Research & Development

Protocol Amendment Approval

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Amendment number:	Malawi-specific Amendment 3
Amendment date:	**22 February 2006**
Approved by: Sponsor Signatory title	[redacted] 01-MAR-2006 dd-mm-yyyy

102248(rota-037)

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Final

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

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Amendment number:	Malawi-specific Amendment 3
Amendment date:	**22 February 2006**

Agreed by:
Investigator: [redacted]

Investigator signature: [redacted]

Date: 24th April 2006

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Malawi-specific Amendment 4
Amendment date:	15 May 2006
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: This Malawi-specific amendment was done on **15 May 2006** to implement the IDMC recommendation dated 03 April 2004.	

Amended text has been indicated in bold italics in the following sections:

Synopsis (Study design) and Section 3

- Study visits: Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). ~~Subjects who undergo HIV testing at Visit 4 will have one additional visit (Visit 5)~~. Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). ***Subjects who undergo the initial HIV testing at Visit 4 may need an additional visit for a confirmatory HIV test (Visit 5 will take place 21-48 days after Visit 4) as well as another contact so that the study staff can inform parents/guardians of the confirmatory HIV test results and offer further counselling.***

  Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=570) and Dose 1 of HRV vaccine or placebo and routine EPI vaccines. ***Pre-test counselling, informed consent for HIV testing and blood sample from all subjects whose parent/guardian gave consent for HIV testing***.

  Visit 2 (Month 1) – Dose 2 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (adverse events (AEs) leading to drop-out and SAEs). ***Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 1 and collection of an additional blood sample from subjects who test HIV positive at Visit 1 and are asymptomatic for a confirmatory HIV test.***

Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Communication of HIV confirmatory test result and offer further counselling for subjects who had a HIV confirmatory test at Visit 2.***

Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***If HIV test was not performed previously, offer pre-test counselling, informed consent for HIV testing and blood sample for HIV testing, if accepted.***

Visit 5 (Month *4* ~~3.5~~) – ***If needed at 21-48 days after Visit 4. Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 4. Collection of an additional blood sample from subjects who test HIV positive at Visit 4 and are asymptomatic for a confirmatory HIV test and planning for informing the parents/guardians about the confirmatory HIV test result in 2 weeks*** ~~only in Subjects with confirmatory HIV testing at Visit 4 – Inform parents/guardians of the confirmatory HIV test's results and offer further counselling~~.

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at the subsequent visit(s) and be performed at any visit up until Visit 4.

- ***Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.***
- ***Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.***
- ***At subsequent visit, inform parents/guardians of the confirmatory HIV test's results and offer further counselling.***

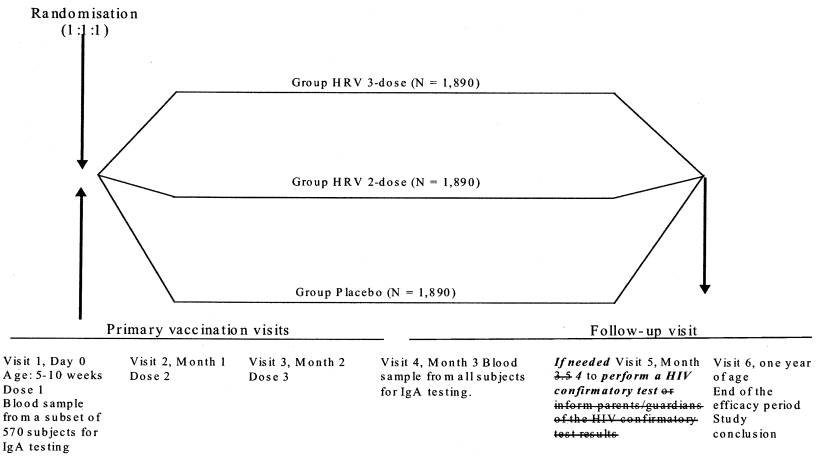
During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing will be proposed at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.

- Blood sample ***will be collected*** from all subjects whose parent/guardian gave ***prior*** consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***at the initial test*** ~~at Visit 3~~ and are asymptomatic.
- Results of HIV testing on blood samples collected ***after informed consent for HIV testing has been obtained*** will be communicated to the parents/guardians at ***the subsequent visit***. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***at the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. ~~If a confirmatory HIV test is done, the~~

~~parents/guardians will have an additional study visit (Visit 5 approximately 2 weeks after Visit 4) so that the study staff can inform them of the confirmatory HIV test results and offer further counselling~~. ***Subjects who undergo the initial HIV testing at Visit 4 may need an additional visit for a confirmatory HIV test (Visit 5) as well as another contact so that the study staff can inform parents/guardians of the confirmatory HIV test results and offer further counselling.*** Results of the HIV test should be recorded in the CRF.

- ~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.
- ***The study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health.***

Section 3



Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Blood sample to be collected from all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample at the subsequent visit from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.

Synopsis (Number of subjects) and Section 4.1

Blood sample ~~at Visit 3~~ from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***after the initial test*** ~~at Visit 3~~ and are asymptomatic.

Section 4.1
A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi.

Section 5.2
Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit ~~3~~ ***1.***

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Pre-test counselling and informed consent for HIV testing will be performed. A blood sample will be obtained from all subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on ***collected*** blood samples will be communicated to the parents/guardians at ***the subsequent visit***. Post-test counselling will be offered to mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***after the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. Results of the HIV test should be recorded in the CRF. ~~If a confirmatory HIV test is done, the parents/guardians have to return for Visit 5 (approximately two weeks after Visit 4) so that the study staff can inform them of the HIV test results and offer further counselling.~~ ***Subjects who undergo the initial HIV testing at Visit 4 may need an additional visit for a confirmatory HIV test (Visit 5) as well as another contact so that the study staff can inform parents/guardians of the confirmatory HIV test results and offer further counselling***.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing will be ***proposed at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ~~at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

The study staff will provide cotrimoxazole prophylaxis to study subjects who are HIV exposed and/or HIV positive for the duration of study follow-up. At study end, subjects will be referred to the cotrimoxazole service provided by the Ministry of Health.

CONFIDENTIAL 102248(rota-037)
Malawi-specific Amendment 4: 15 May 2006

Section 5.4

Age	5-10 weeks					
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6
Timing	Day 0	Month 1	Month 2	Month 3	Month ~~3~~ 4	1 year of age
Sampling timepoint	Pre		~~Post vacc 2~~	Post vacc 3		
Informed consent addendum for HIV testing	•		•	•		
Medical history for HIV	#•		•			
For HIV testing, ***if and when accepted‡***	•		~~• (3 ml in South Africa and 1 ml in Malawi) in subjects whose parent/ guardian has given consent at Visit 3~~	~~•• (2 ml in South Africa and 1 ml in Malawi) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test~~		
Confirmatory HIV testing, if required		•			•	
Record results of HIV testing		•	•	•	•	
Inform subjects of HIV result		•	•	•	•	

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries ***(See Section 5.5 and Section 5.6.2).***

†***Visit 5 will take place 21-48 days after Visit 4*** only in subjects ***needing a*** confirmatory HIV test

‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit.

Table 2 Intervals between study visits

Interval	Size of interval
4 (Visit 4→Visit 5)	***21*** ~~7~~ to 48 days

Section 5.5

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- ***Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.***
- ***Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent.***

When materials are provided by GSK Biologicals or designated laboratory, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for

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

- ***Record results of the HIV test at the subsequent visit in the CRF.***
- ***Only in subjects who test HIV positive at the initial test and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test.***

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the confirmatory HIV test at the subsequent visit in the CRF.***
- ***Communicate HIV test result of the confirmatory HIV test to parents/guardians at the subsequent visit and post-test counselling.***

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- ***Proposal for HIV testing to parents/guardians. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ***Record medical history with regards to HIV exposure in the CRF.***

Visit 2, Month 1, Dose 2 (28-48 days after Visit 1)
(Amendment 2: 27 October 2005)

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling and collection of blood samples for confirmatory HIV test if required.***

Visit 3, Month 2, Dose 3 (28-48 days after Visit 2)
(Amendment 2: 27 October 2005)

- ***If confirmatory HIV test done at the preceding visit, communicate the results of the HIV to parents/guardians, record results of HIV test in the CRF and post-test counselling.***
- ~~Record medical history with regards to HIV exposure in the CRF. (Amendment 1: 24 August 2005)~~
- ~~Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling. (Amendment 1: 24 August 2005)~~

- ~~Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals or designated laboratory, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E. (Amendment 1: 24 August 2005)~~

- ~~Record results of the HIV test at Visit 3 in the CRF. (Amendment 1: 24 August 2005)~~

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- ***Proposal for HIV testing to parents/guardians, if HIV testing not done previously. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ~~Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling. (Amendment 1: 24 August 2005)~~.
- ~~Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.~~

- ~~Record results of the HIV test at Visit 4 in the CRF. (Amendment 1: 24 August 2005)~~

***If needed,* Visit 5, Month *4* ~~3.5,~~ Follow-up (~~7~~*21*- 48 days after Visit 4) Only for subjects who needed confirmatory HIV testing**

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling, collection of blood samples for confirmatory HIV test if required and planning for***

a contact to inform the parents/guardians about the confirmatory HIV test result in 2 weeks.

Section 5.6.2

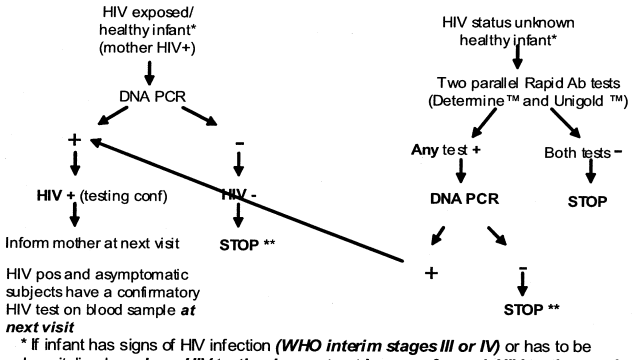
Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

HIV testing ~~at Visit 3~~ will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at ***the initial test*** ~~Visit 3~~ and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit*** ~~Visit 4~~.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing will be ***proposed at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

Malawi

Subjects who test HIV positive at ***the initial test*** ~~Visit 3~~ and are asymptomatic will undergo PCR testing ***at the time of the confirmatory test*** ~~Visit 4~~.



* If infant has signs of HIV infection ***(WHO interim stages III or IV)*** or has to be hospitalised, ***and any HIV testing has not yet been performed, HIV testing and the concerned Informed Consent will be proposed to the mothers***

** If breast-feeding : repeat test at 3 months after breast-feeding cessation.

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	Month	Visit no			
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
HIV test			Serum HIV antibody test (ELISA)	Subjects not exposed to HIV or HIV status unknown	None
			Whole blood DNA PCR	- Subjects not exposed to HIV and positive for HIV antibody - Subjects exposed to HIV	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at Visit 3 and asymptomatic	None
Malawi					
HIV test			rapid HIV antibody tests	All	None
			Whole blood DNA PCR	Subjects positive by any of the two rapid HIV antibody tests or in case of discrepancy	None
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR at ***the initial HIV test*** ~~Visit 3~~ and asymptomatic	None

Section 8.4 and Section 8.7

~~If not yet performed, HIV testing will be encouraged at hospital admission, and the results should be recorded in the CRF. (Amendment 1: 24 August 2005)~~ ***During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing will be proposed by the study staff at hospital admission. HIV testing performed at hospital admission should be recorded in the CRF.***

Section 8.12

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

Appendix C

- A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi. Enrolment will be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa and a minimum of 2670 subjects to be enrolled in Malawi.
- ~~All subjects will be enrolled within a period of 3 months.~~ ***Subjects in Malawi will be enrolled within a period of 6 to 8 months.***

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Malawi-specific amendment 4
Amendment date:	15 May 2006
Approved by: Sponsor Signatory title	[redacted] 30-MAY-2006 dd-mm-yyyy

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-Track #
Rota – 037	102248

Date: 29MAY2008

Details:

This file note serves to document the following:

- Protocol Administrative Change 2, 30AUG2007: The investigators have signed on a protocol agreement version before QC (formatting QC). Even though it's the wrong page signed, the signatures are still valid.
- Protocol South Africa Specific Amendment 5, 10JUL2006: On the approval page of the investigator agreement, the cars footer was missing for the sign off of Dr. [redacted] Even though the cars footer is missing, the investigator signed the final version of the protocol.
- Protocol Malawi Specific Amendment 4, 15MAY2006: On the approval page of the investigator agreement, the cars footer was missing for the sign off of Dr. [redacted] Even though the cars footer is missing, the investigator signed the final version of the protocol.

This file note provides an official record of this process:

File note created by: [redacted] **(GSM)** **Signature:** [redacted]

Signature Date: 30 May 2008

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GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Malawi-specific amendment 4
Amendment date:	15 May 2006
Agreed by:	
Investigator:	DR [redacted]
Investigator signature:	
Date:	26 SEP '06

CONFIDENTIAL 102248(rota-037)
South Africa-specific Amendment 5: 10 July 2006

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	**10 July 2006**
Co-ordinating author:	[redacted] Scientific Writer
Rationale/background for changes: This South Africa-specific amendment was done on **10 July 2006** to implement the IDMC recommendation dated 03 April 2004 for the subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa).	

Amended text has been indicated in bold italics in the following sections:

List of abbreviations

PMTCT	***Prevention of Mother To Child Transmission***

Definitions

- RV season in South Africa: Based on epidemiological observations, the RV season will be considered during the period from March 01 to ~~June 30~~ ***July 31*** in South Africa.

Synopsis (Study design) and Section 3

- ***Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa.***
- Study visits: Study visits: All subjects will have five study visits (Visit 1, 2, 3, 4 and 6). Subjects who undergo ***initial*** HIV testing at Visit 4 will have one additional visit (Visit 5 ***at 21-48 days after Visit 4) to communicate results of the initial HIV test to the parents/guardians. If required, a confirmatory HIV test may be performed at***

Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling.

Visit 1 (Day 0) – Pre-vaccination blood sample from a subset of subjects (N=570 ***Not from cohort 2 in South Africa***) and Dose 1 of HRV vaccine or placebo and routine EPI vaccines. ***Pre-test counselling, informed consent for HIV testing and blood sample from all subjects whose parent/guardian gave consent for HIV testing***.

Visit 2 (Month 1) – Dose 2 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (adverse events (AEs) leading to drop-out and SAEs). ***Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 1 and collection of an additional blood sample from subjects who test HIV positive at Visit 1 and are asymptomatic for a confirmatory HIV test.***

Visit 3 (Month 2) – Dose 3 of HRV vaccine or placebo and routine EPI vaccines, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***Communication of HIV confirmatory test result and offer further counselling for subjects who had a HIV confirmatory test at Visit 2.***

Visit 4 (Month 3) – Post-vaccination blood sample from all subjects, follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples and follow-up for safety (AEs leading to drop-out and SAEs). ***If HIV test was not performed previously, offer pre-test counselling, informed consent for HIV testing and blood sample for HIV testing, if accepted.***

Visit 5 (Month ***4*** ~~3.5~~) – ***At 21-48 days after Visit 4, o***nly in subjects with ~~confirmatory~~ ***initial*** HIV testing at Visit 4***. Post-test counselling for mothers or guardians of all subjects whose parents/guardian gave consent for HIV testing at Visit 4. Collection of an additional blood sample from subjects who test HIV positive at Visit 4 and are asymptomatic for a confirmatory HIV test and planning for informing the parents/guardians about the confirmatory HIV test result in 2 weeks***. ~~– Inform parents/guardians of the confirmatory HIV test's results and offer further counselling~~. (Amendment 1: 24 August 2005)

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- ***Pre-test counselling and informed consent for HIV testing. Blood sample from all subjects whose parent/guardian gave consent for HIV testing.***
- ***Post-test counselling for mothers or guardians of all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.***
- ***At subsequent visit/contact, inform parents/guardians of the confirmatory HIV test's results and offer further counselling.***

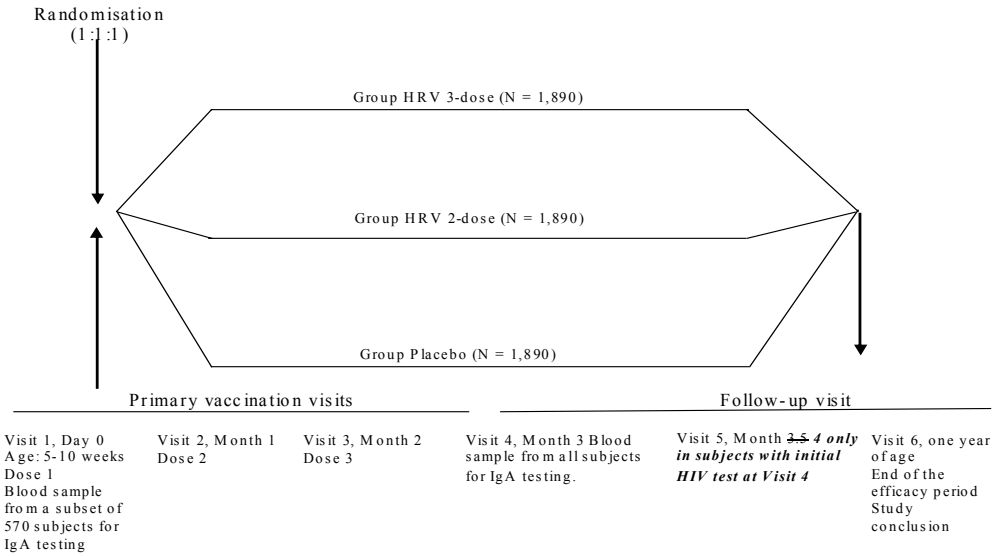
During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.

- Blood samples will be collected from a subset of subjects (N=570 subjects; ***not from subjects in cohort 2 in South Africa***) at Visit 1 and from all subjects at Visit 4 to measure anti-rotavirus IgA antibodies.
- Blood sample ***will be collected*** from all subjects whose parent/guardian gave ***prior*** consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***at the initial test*** ~~at Visit 3~~ and are asymptomatic.
  - Study staff will visit the subject every week to check for occurrence of any diarrhoea during the entire study period.
- Results of HIV testing on blood samples collected ***after informed consent for HIV testing has been obtained*** will be communicated to the parents/guardians at ***the subsequent visit/contact***. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***at the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. If ***an initial*** ~~confirmatory~~ HIV test is done ***at Visit 4***, ~~the parents/guardians will have~~ ***there will be*** an additional study visit (Visit 5 ~~approximately 2 weeks~~ ***21-48 days*** after Visit 4) so that the study staff can inform ***parents/guardians of HIV test results*** and offer ~~further~~ ***post-test*** counselling. ***If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling.*** Results of the HIV test should be recorded in the CRF.
- In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] and Standard of Care provided during GSK sponsored trials.
- ~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1

or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed (due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

Section 3



Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Blood sample to be collected from all subjects whose parent/guardian gave consent for HIV testing. Collection of an additional blood sample at the subsequent visit from subjects who test HIV positive and are asymptomatic for a confirmatory HIV test.

Synopsis (Number of subjects) and Section 4.1

No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1.

Blood sample ~~at Visit 3~~ from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***after the initial test*** ~~at Visit 3~~ and are asymptomatic.

Section 4.1

A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi. Enrolment will ***continue until a total of 5670 subjects are enrolled in the study*** ~~be competitive up to December 2005 with a maximum~~

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~~of 3,000 subjects to be enrolled in South Africa and a minimum of 2670 subjects to be enrolled in Malawi~~

As of January 2006 a total of 1,827 subjects have been enrolled in South Africa (Cohort 1 in South Africa). Enrolment in South Africa was suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa shall resume after the RV season to enrol the total planned number of subjects (Cohort 2 in South Africa).

No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1.

Blood sample ~~at Visit 3~~ from all subjects whose parent/guardian gave consent for HIV testing. An additional blood sample will be collected for a confirmatory HIV test at ***the subsequent visit*** ~~Visit 4~~ from subjects who test HIV positive ***after the initial test*** ~~at Visit 3~~ and are asymptomatic.

Section 4.2

- Written informed consent obtained from the parent or guardian of the subject ***who is of legal age (i.e. parent/guardian should be 18 years or older)***.
- ***In South Africa, birth weight > 2000 g or if weight unknown, gestation period > 36 weeks.***

Section 5.1.2

In addition to the Informed Consent Form at Visit 1 to participate in this study, parents/guardians will be presented with ***an informed consent form summary and a feedback form as well as*** a second Informed Consent Form to obtain consent for HIV testing of the subjects. ***The HIV test will be proposed and ideally performed at visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible.***

Section 5.2

Changes to the protocol pertaining to the South Africa-specific Amendment 5 dated 10 July 2006 will apply to subjects who shall be enrolled in South Africa when recruitment resumes (Cohort 2 in South Africa). Refer to Annex 3 for description of study visits for cohort 1 enrolled in South Africa.

Medical history with regards to exposure of the subject to HIV will be recorded in the CRF at Visit ~~3~~ ***1.***

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. Pre-test counselling and informed consent for HIV testing will be performed. A blood sample will be obtained from all

subjects whose parent/guardian gave consent for HIV testing. Results of HIV testing on ***collected*** blood samples will be communicated to the parents/guardians at ***the subsequent visit/contact***. Post-test counselling will be offered to mothers or guardians of study subjects who consented for HIV testing. For subjects who test HIV positive ***after the initial test*** and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit***. Results of the HIV test should be recorded in the CRF. ~~If a confirmatory HIV test is done, the parents/guardians have to return for Visit 5 (approximately two weeks after Visit 4) so that the study staff can inform them of the HIV test results and offer further counselling.~~ ***Subjects who undergo the initial HIV testing at Visit 4 will have an additional visit so that the study staff can inform parents/guardians of HIV test results and offer post-test counselling. If required, a confirmatory HIV test may be performed at Visit 5 and a contact would be planned to inform the parents/guardians about the confirmatory HIV test result in 2 weeks and offer further counselling***.

In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] and Standard of Care provided during GSK sponsored trials.

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ~~at Visit 3~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing ***will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

In South Africa, cotrimoxazole prophylaxis will be prescribed for all subjects who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If the subject is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If the subject is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centers to which they have been referred. Subjects who are HIV negative and still HIV exposed

(due to breast feeding) will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

National Guidelines in South Africa recommend HIV testing ~~3 months~~ ***6 weeks*** after breast feeding cessation ~~which usually corresponds to 9 months old~~. ***This testing will be done through the usual clinic/paediatric outpatient system.*** The results of repeat test after breast feeding ceases ~~in HIV exposed subjects in South Africa who were negative at Visit 3~~ should be recorded in the CRF.

- GE surveillance:

  Study staff will visit the subject every week to check for the occurrences of any GE during the entire study period.

The study staff will direct the parents/guardians to the nearest hospital/medical facility ~~for~~ as necessary.

Section 5.4

Table 1 List of study procedures *for cohort 2 enrolled in South Africa and all subjects enrolled in Malawi*

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month ~~3~~ *4***	**1 year of age**
Sampling timepoint	**Pre**		**~~Post vacc 2~~**	**Post vacc 3**		
Informed consent addendum for HIV testing*†*	•		~~•~~	•		
Medical history for HIV	#•		~~•~~			
For HIV testing, ***if and when accepted‡***	***• (3 ml in South Africa and 1 ml in Malawi)***		~~• (3 ml in South Africa and 1 ml in Malawi) in subjects whose parent/ guardian has given consent at Visit 3~~	***• (3 ml in South Africa and 1 ml in Malawi)*** ~~• (2 ml in South Africa and 1 ml in Malawi) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test~~		
Confirmatory HIV testing, if required		***• (2 ml in South Africa and 1 ml in Malawi)***			***• (2 ml in South Africa and 1 ml in Malawi)***	
Record results of HIV testing		•	•	~~•~~	•	
Inform subjects of HIV result		•	•	~~•~~	•	

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The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries ***(See Section 5.5 and Section 5.6.2).*** (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006)

†***Visit 5 will take place 21-48 days after Visit 4 o***nly in subjects ***who had an initial HIV test at Visit 4*** ~~needing a confirmatory HIV test~~

‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit.

†During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.

Table2 Intervals between study visits *for cohort 2 enrolled in South Africa and all subjects enrolled in Malawi*

Interval	Size of interval
4 (Visit 4→Visit 5)	***21*** ~~7~~ to 48 days

Refer to Annex 3 for list of study procedures and intervals between study visits for cohort 1 enrolled in South Africa.

Section 5.5

Cohort 1 enrolled in South Africa

Refer to Annex 3 for detailed description of study visits for cohort 1 enrolled in South Africa.

Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

- ***Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling.***
- ***Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent.***

When materials are provided by GSK Biologicals or designated laboratory, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the HIV test at the subsequent visit in the CRF.***

- ***Only in subjects who test HIV positive at the initial test and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test.***

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.

- ***Record results of the confirmatory HIV test at the subsequent visit/contact in the CRF.***
- ***Communicate HIV test result of the confirmatory HIV test to parents/guardians at the subsequent visit/contact and post-test counselling.***

Visit 1, Day 0: 5-10 weeks of age, Dose 1

- ***Proposal for HIV testing to parents/guardians. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ***Record medical history with regards to HIV exposure in the CRF.***

Visit 2, Month 1, Dose 2 (28-48 days after Visit 1)

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling and collection of blood samples for confirmatory HIV test if required.***

Visit 3, Month 2, Dose 3 (28-48 days after Visit 2)

- ***If confirmatory HIV test done at the preceding visit, communicate the results of the HIV to parents/guardians, record results of HIV test in the CRF and post-test counselling.***
- ~~Record medical history with regards to HIV exposure in the CRF. (Amendment 1: 24 August 2005)~~
- ~~Written informed consent from the parent/guardian of the subject to perform HIV testing and pre-test counselling. (Amendment 1: 24 August 2005)~~
- ~~Collection of whole blood (3 ml in South Africa and 1 ml in Malawi) for HIV testing from subjects whose parents/guardians gave consent. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals or designated laboratory, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and~~

~~stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E. (Amendment 1: 24 August 2005)~~

- ~~Record results of the HIV test at Visit 3 in the CRF. (Amendment 1: 24 August 2005)~~

Visit 4, Month 3, Follow-up (30-48 days after Visit 3)

- ***Proposal for HIV testing to parents/guardians, if HIV testing not done previously. If proposal for HIV testing accepted, pre-test counselling, informed consent for HIV testing and blood sample from subjects whose parent/guardian gave consent for HIV testing.***
- ~~Communicate the results of the HIV test at Visit 3 to parents/guardians and post-test counselling. (Amendment 1: 24 August 2005)~~.
- ~~Only in subjects who test HIV positive at Visit 3 and are asymptomatic: Collection of whole blood (2 ml in South Africa and 1 ml in Malawi) for a confirmatory HIV test. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005)~~

~~When materials are provided by GSK Biologicals, it is **MANDATORY** that all clinical samples (including serum samples) will be collected and stored using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing biological samples, then appropriate materials from the investigator's site are to be used. Refer to Appendix D and Appendix E.~~

- ~~Record results of the HIV test at Visit 4 in the CRF. (Amendment 1: 24 August 2005)~~

Visit 5, Month *4* ~~3.5,~~ Follow-up (~~7~~*21*- 48 days after Visit 4) Only for subjects who ~~needed confirmatory HIV testing~~ *had initial HIV test at Visit 4*

- ***If HIV testing done at the preceding visit, communicate the results of the HIV test to parents/guardians, record results of HIV test in the CRF, post-test counselling, collection of blood samples for confirmatory HIV test if required and planning for a contact to inform the parents/guardians about the confirmatory HIV test result in 2 weeks.***

Section 5.6.2

GE Stool analysis

All stool samples collected during diarrhoea episodes from Visit 1 to Visit 6 will be processed at the study site ***or designated laboratory*** and shipped frozen to GSK Biologicals, Belgium.

HIV assay

Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4.

HIV testing ~~at Visit 3~~ will be performed in subjects whose parent/guardian gave consent. For subjects who test HIV positive at ***the initial test*** ~~Visit 3~~ and are asymptomatic, a confirmatory HIV test should be performed at ***the subsequent visit*** ~~Visit 4~~.

During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO ***interim*** stages III ***or IV***), or has to be hospitalised ***with SAE and any HIV testing has not yet been performed***, HIV testing ***will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.*** ~~proposed to the mothers before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.~~

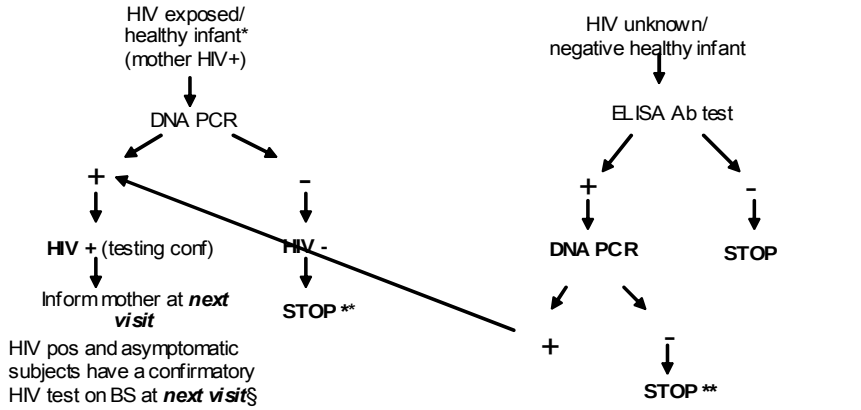
South Africa

HIV testing will be done according to the algorithm presented in Figure 1 (see below) based on the guidelines HIV testing guidelines in children from the Department of Health, South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] as outlined in Annex 2.

National Guidelines in South Africa recommend HIV testing ~~3 months~~ ***6 weeks*** after breast feeding cessation ~~which usually corresponds to 9 months old~~. ***This testing will be done through the usual clinic/paediatric outpatient system.*** The results of the repeat test after breast feeding ceases should be recorded in the CRF.

In case of discrepancy between HIV test results at ***initial and confirmatory tests*** ~~Visit 3 and Visit 4~~ (HIV positive at ***initial test*** ~~Visit 3~~, negative at ***confirmatory test*** ~~Visit 4~~), the HIV test should be repeated on the ***confirmatory test***~~Visit 4~~ blood sample If the discrepancy remains, the child should be sent to an ARV roll out center for HIV repeat test on a new blood sample according to National Guidelines in South Africa.

Figure 3 Algorithm for HIV testing in South Africa



* If infant has signs of HIV infection or has to be hospitalized ***(WHO interim stages III and IV) and any HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible***
** In South Africa: If breast-feeding : repeat test ***6 weeks*** after breast-feeding cessation
§ documented study contact ***for subjects with confirmatory HIV test***

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	**Month**	**Visit no**			
HIV assay in subjects whose parent/guardian gave consent					
South Africa					
Confirmatory HIV test			Whole blood DNA PCR	Subjects HIV positive by DNA PCR ***at the initial HIV test*** ~~Visit 3~~ and asymptomatic	None

In South Africa, based on the result of the HIV assay, access to further testing, treatment or counselling will be available to subjects in South Africa as per the national guidelines in South Africa ***[South African National Department of Health Guidelines for the Management of HIV-infected Children 2005]*** (also refer to Section 5.2).

Section 6.2

Should the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered at that visit. The subject may continue to participate ~~to~~ ***in*** the study and will not be excluded from the planned analyses.

Section 6.4.1

To allow GSK Biologicals to take advantages of greater rates of recruitment than anticipated at individual centres in this multicenter study, and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

Section 6.4.3

No subjects from cohort 2 in South Africa will be part of the subset providing blood samples at Visit 1.

Section 6.5

A set of individual codes will be held at the ~~local GSK Biologicals' Safety Office and~~ GSK Biologicals' Central Safety Office. ~~If there is no local Safety Office, a set of individual codes will be held by the Medical Monitor.~~

Section 8.4 and Section 8.7

~~If not yet performed, HIV testing will be encouraged at hospital admission, and the results should be recorded in the CRF. (Amendment 1: 24 August 2005)~~ ***During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.***

Section 8.12

In South Africa, procedures to be followed for anti-retroviral (ARV) therapy will be in compliance with national guidelines in South Africa [~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***South African National Department of Health Guidelines for the Management of HIV-infected Children 2005***] and Standard of Care provided during GSK sponsored trials.

~~GSK Biologicals~~ ***The study staff*** will, ***where clinically indicated and/or for hospitalised HIV positive children,*** facilitate access ***of study subjects*** to ***a HIV staging facility and/or*** ARV treatment centers ~~for any children who test HIV positive~~ ***during the study***, but decisions towards treatment will be taken by appropriate staff at these treatment centers.

Section 10.6.1

HIV status at Visit ~~3~~ ***1*** and Visit 4 will be presented.

Appendix A

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

Appendix C

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- A minimum of 2,600 subjects will be enrolled in South Africa and ***a maximum of*** 3070 subjects will be enrolled in Malawi. Enrolment will ***continue until a total of 5670 subjects are enrolled in the study*** ~~be competitive up to December 2005 with a maximum of 3,000 subjects to be enrolled in South Africa and a minimum of 2670 subjects to be enrolled in Malawi~~.
- ***As of January 2006 a total of 1,827 subjects have been enrolled in South Africa (Cohort 1 in South Africa). Enrolment in South Africa was suspended to allow vaccination to be completed before the start of the RV season. Enrolment in South Africa shall resume after the RV season to enrol the total planned number of subjects (Cohort 2 in South Africa).***

Appendix D

3. Preparation of aliquot

- Stool samples collected during specified timepoints and gastroenteritis episodes will be processed, at the study site ***or designated laboratory***, to prepare an aliquot in a 8 ml tube.

Annex 2

Source: ~~National Antiretroviral Treatment Guidelines, First Edition, 2004~~ ***Guidelines for the Management of HIV-infected Children 2005***. Accessed on the website ~~http://www.doh.gov.za/search/index.html~~ ***http://www.doh.gov.za/docs/factsheets/guidelines/hiv/index.html.***

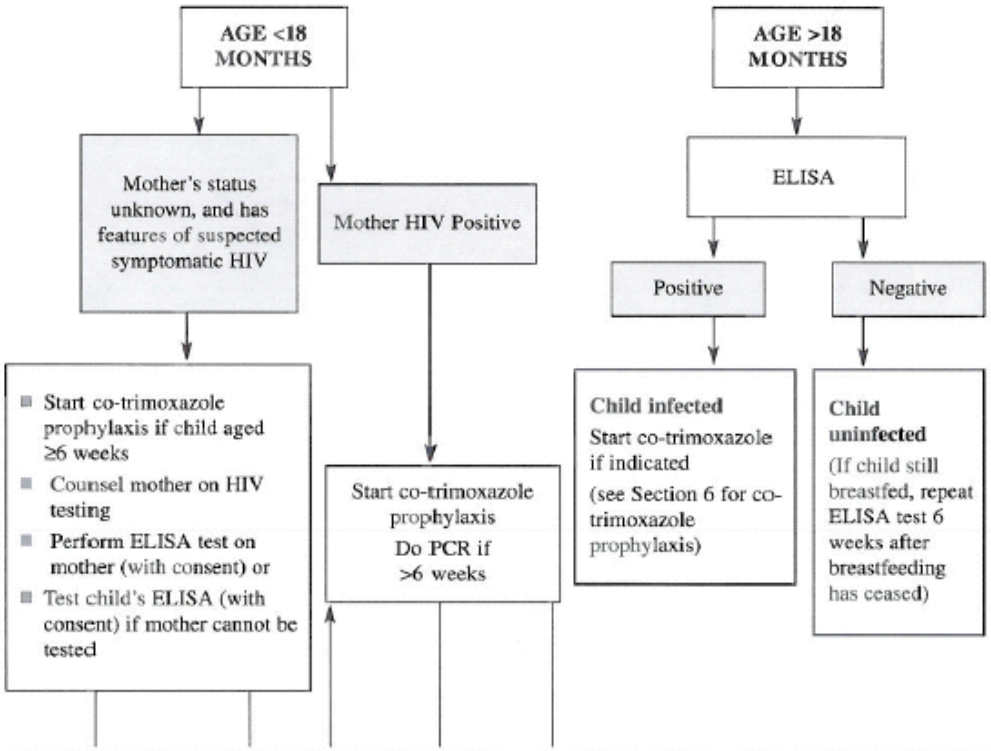

Figure 1: HIV testing guidelines

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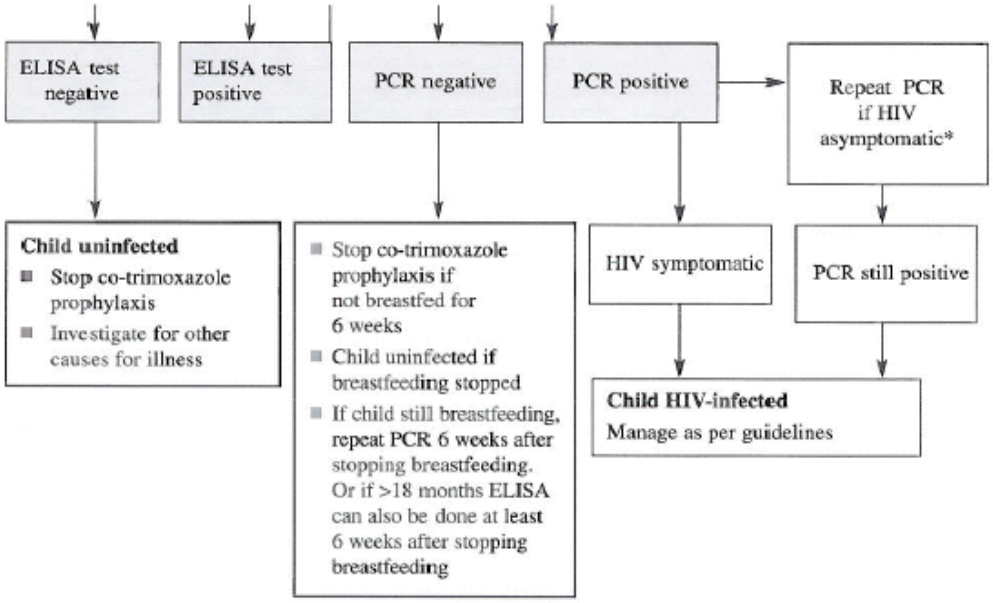
South Africa-specific Amendment 5: 10 July 2006



Note: *Contact laboratory if results are discrepant.
PCR testing may not be available at all centres immediately.
In the absence of PCR, perform HIV ELISA testing at 12 and, if positive, at 18 months.
PCR = HIV DNA PCR
ELISA = HIV ELISA

Annex 3

Annex 3 Study procedures for cohort 1 enrolled in South Africa as per Amendment 2 dated 27 October 2005 was added.

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South Africa-specific Amendment 5: 10 July 2006

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Approved by: Director (for) [redacted]	19-07-2006 dd-mm-yyyy

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Agreed by:	
Investigator:	[redacted]
Investigator signature:	[redacted]
Date:	2 AUGUST 2006.

[redacted]

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment Approval**	
eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Agreed by: **Investigator:** **Investigator signature:** **Date:**	[redacted] 31 JUL 2006

29 May 2008 15:38 [redacted] [redacted] p.3

2008 May 29 13:07 [redacted] [redacted] p.4

FILE NOTE

PROTOCOL NUMBER: 102248/037 **SPONSOR: GSK**

DATE FILE NOTE GENERATED:	29 May 2008
GENERATED BY:	[redacted] / Dr [redacted]
SIGNATURE: [redacted]	[redacted]
DESIGNATION:	Site Manager / PI

Re: Amendment 5 - Investigator Approval Signature Page

Dr [redacted] - Principal Investigator at Center [redacted] was on maternity leave, when Amendment 5 was distributed to the sites.

As such the Investigator Approval Signature Page was signed by Dr [redacted] - Sub investigator.

CLINICAL RESEARCH DEPT.
29 MAY 2008
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29 May 2009 15:37 [redacted] [redacted] p.1

2008 May 29 13:07 [redacted] [redacted] p.2

CONFIDENTIAL 102248(rota-037)
South Africa-specific Amendment 3: 10 July 2006

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

GSK study number	102248
Short abbreviated title	rota-037
Protocol title	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2: 27 October 2005)
Amendment number:	South Africa-specific amendment 3
Amendment date:	10 July 2006
Agreed by: Investigator:	[redacted]
Investigator signature:	
Date:	29 MAY 2008

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29 MAY 2008
CLINICAL RESEARCH DEPT.

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File Note

Alias / Abbreviated Study Title	CPMS / E-track #
Rota-037 (South Africa)	102248

Date: 18 March 2009

Concerns: **Amendment 5 and 6 Investigator Signature Page**

Details:

Dr [redacted] signed the correct version of the Investigator Signature page for Amendment 5 that is in the files although the CARS footer is missing.

Doctors [redacted] and [redacted] have all signed the correct version of the Amendment 6 Investigator Signature page although the checksum is missing.

GSM Responsible: [redacted]

Signature: [redacted]

Signature Date: MAR 18 2009

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File Note

Alias / Abbreviated Study Title	CPMS / E-Track #
Rota – 037	102248

Date: 29MAY2008

Details:

This file note serves to document the following:

- Protocol Administrative Change 2, 30AUG2007: The investigators have signed on a protocol agreement version before QC (formatting QC). Even though it's the wrong page signed, the signatures are still valid.
- Protocol South Africa Specific Amendment 5, 10JUL2006: On the approval page of the investigator agreement, the cars footer was missing for the sign off of Dr. [redacted] Even though the cars footer is missing, the investigator signed the final version of the protocol.
- Protocol Malawi Specific Amendment 4, 15MAY2006: On the approval page of the investigator agreement, the cars footer was missing for the sign off of Dr. [redacted] Even though the cars footer is missing, the investigator signed the final version of the protocol.

This file note provides an official record of this process:

File note created by: [redacted] **(GSM)** **Signature:** [redacted]

Signature Date: 30 May 2008

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Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Agreed by:	
Investigator:	[redacted]
Investigator signature:	
Date:	22/Mar/2007

22. Mar. 2007 16:39 [redacted] No. 1772 P. 3

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
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Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006

Agreed by:
Investigator: [redacted]

Investigator signature: [redacted]

Date: 15/08/06.

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
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Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Agreed by: **Investigator:** Dr [redacted]	
Investigator signature:	
Date: 13 August 2006	

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
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Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Agreed by:	
Investigator:	[redacted]
Investigator signature:	[redacted]
Date:	31/07/06

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006

Agreed by:
Investigator:

Investigator signature: [redacted]

Date: 21 Aug 2006

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006

Agreed by:
Investigator: Dr [redacted]

Investigator signature: [redacted]

Date: 24 Nov 2006

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102248
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Amendment number:	South Africa-specific amendment 5
Amendment date:	10 July 2006
Agreed by:	Dr [redacted]
Investigator:	[redacted]
Investigator signature:	[redacted]
Date:	17 Aug 2006

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Clinical Research & Development

Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	Rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Amendment 6
Amendment date:	**2 August 2007**
Co-ordinating authors:	[redacted] Scientific Writers

Rationale/background for changes: This amendment was done on 2 August 2007 to implement the following changes for the South Africa cohort as recommended by the Rotavirus Vaccine Program (RVP) organization which co-sponsors this study.

- To perform an interim analysis on efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. This interim analysis is performed under the request by RVP to allow early review of African efficacy data to prepare implementation of universal mass vaccination (UMV) in some African countries. The availability of earlier results suggesting favourable efficacy of the vaccine in developing countries in Africa would be useful as an advocacy tool to stimulate policy makers both at global level (e.g. WHO, SAGE, GAVI) and at the country level to prepare for accelerated decision-making and introduction activities in Africa.
- To extend follow-up for efficacy until the end of the second consecutive RV season for Cohort 2 South Africa. Also, safety follow-up for SAEs and AEs leading to drop out will be performed for these subjects until the end of the RV season. The follow-up during the second year will also be performed for the cohort in Malawi. Additional follow-up may allow for the estimation of vaccine efficacy, either among all infants over the combined first and second year of life or during the second year of life. Additional follow-up may also provide greater power to investigate other aspects of vaccine efficacy such as protection among infants in these populations with high HIV prevelance, better estimation of strain and dose-specific vaccine efficacy.
- To implement a supplementary ICF to allow using post-breast feeding cessation HIV results in the analysis when HIV test is performed.

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- To implement administrative changes to update the study team in GSK Biologicals, Rixensart.
- The sample size of the study population was adjusted as the actual number of RV GE episodes reported so far indicated that the initially planned incidence of 1.5% for severe RV GE cases in the placebo group during the first efficacy period was too conservative. Hence, the incidence rate was revised and a 2% incidence rate has been considered. Thus, the total number of subjects to be enrolled in the study has been decreased.

Amended text has been indicated in bold italics in the following sections:

Title page (Co-ordinating authors)

[redacted] Scientific Writer***s***

Title page (Contributing authors)

[redacted] Director

[redacted] Central Study Coordinator

[redacted] Clinical Development Manager

Sponsor signatory: [redacted] Director

List of Abbreviations

RVP Rotavirus Vaccine Program

Glossary of Terms

Efficacy follow-up period: ~~All subjects will be followed until one year of age.~~ ***S***ubjects ***in Cohort 1 South Africa*** will be followed until one year of age. ***Subjects in Cohort 2 South Africa will continue efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).***

Synopsis (Definitions)

Efficacy follow-up period: ~~All~~ ***S***ubjects ***in Cohort 1 South Africa*** will be followed until one year of age. ***Subjects in Cohort 2 South Africa will continue efficacy and safety follow-up until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).***

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Synopsis (References)

Cunliffe NA, Kilgore PE, Bresee JS, et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. Bull World Health Organ. 1998;76:525-37.

De Zoysa I, Feachem RV. Intervention for the control of diarrheal disease among children: rotavirus and cholera immunization. Bull World Health Organ. 1985;63:569-83.

Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis. 1990; 22:259-67.

Steele AD, Peenze I, de Beer MC, et al. Anticipating rotavirus vaccines: epidemiology and surveillance of rotavirus in South Africa. Vaccine. 2003;21:354-60.

Synopsis (secondary objectives) and Section 2.2

For subjects in Cohort 2 South Africa and the cohort in Malawi:

- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE (≥ 11 on the 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***To assess the efficacy against severe RV GE caused by the circulating wild-type RV strains after 3 doses (at 6-10-14 weeks of age) versus 2 doses (at 10-14 weeks of age) of GSK Biologicals' HRV vaccine given concomitantly with routine EPI vaccinations during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7.***
- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***To assess the efficacy of GSK Biologicals' HRV vaccine (pooled HRV groups) given concomitantly with routine EPI vaccinations to prevent severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***

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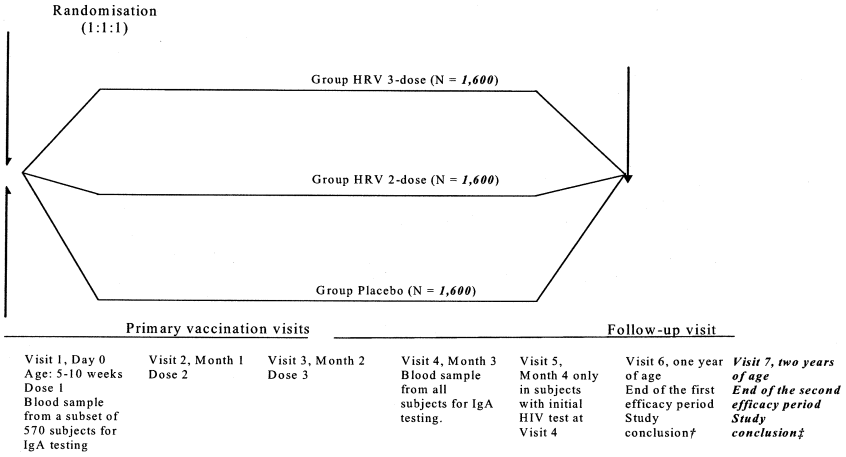
Section 1.1

Please refer to the latest version of the investigator brochure (Edition ~~5~~ ***8***) for a detailed review of other information on the HRV vaccine.

Section 1.2

Although this HRV vaccine is registered in Malawi and ***South Africa, and*** will become available in the private market; a placebo controlled trial is justified as the vaccine is not available through public health care programmes to the general population.

Section 3



† For subjects in Cohort 1 South Africa
‡ For subjects in Cohort 2 South Africa and the Cohort in Malawi

Synopsis (study design) and Section 3

- Treatment Groups:
  - Group HRV 3-Dose: 3 doses of HRV given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N = ~~1,890~~ ***1,600***)
  - Group HRV 2-Dose: 2 doses of HRV given concomitantly with routine EPI vaccines at 10 and 14 weeks of age. (Placebo dose will be given concomitantly with routine EPI vaccines at 6 weeks of age to maintain the double blinding) (N = ~~1,890~~ ***1,600***)
  - Group Placebo: 3 doses of placebo given concomitantly with routine EPI vaccines at 6, 10 and 14 weeks of age (N = ~~1,890~~ ***1,600)***

For subjects in Cohort 2 South Africa, efficacy and safety follow-up will continue until the end of the RV season in 2008 (between 1 August 2008 and 15 September

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2008). For all subjects in Malawi, efficacy and safety follow-up will continue until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009). These subjects will have an additional visit i.e. Visit 7.

Visit 6 (at one year of age) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) ***for subjects in Cohort 1 and 2 in South Africa and the Cohort in Malawi*** and study conclusion ***for all the subjects in Cohort 1 South Africa. A supplementary ICF will be provided to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed. A supplementary ICF will be provided to the parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi to request their child's/ward's participation in the second year follow-up for this study.***

Visit 7, only for subjects in Cohort 2 South Africa (at the end of the RV season in 2008 i.e. between 1 August 2008 and 15 September 2008) and for all subjects in the Cohort in Malawi (until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009) – Follow-up for GE episodes with return of any GE diary cards and/or diarrhoeal stool samples, follow-up for safety (AEs leading to drop-out and SAEs) and study conclusion.

Results of HIV test conducted post-breast feeding cessation will be recorded in the CRF when consent to do so has been obtained from the subject's parents/guardians.

During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and*** from Visit 1 up until Visit *7* ***for subjects in Cohort 2 South Africa***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed ***at the site*** or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa, HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics or hospitals, as indicated as per clinical symptoms.*** HIV testing performed at hospital admission should be recorded in the CRF.

- Recording of height and weight at Visit 1, Visit 4, Visit 6 and ***Visit 7***.
- Active follow-up for occurrence of GE episodes (diarrhoea) via weekly visit to a subject by study personnel during the entire study period (from the day of Dose 1 until Visit 6 ***for subjects in Cohort 1 South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***)).
- ***Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period. Results of the analysis for efficacy and***

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safety data collected during the second efficacy follow-up period will be provided in an annex report.

- ***An interim analysis on vaccine efficacy against severe RV GE and any RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind.***
- Duration of the study: The study subjects ***in Cohort 1 in South Africa*** will be followed until one year of age, ***and the*** intended duration of the study, per subject, will not exceed a maximum of 10 to 11 months. ***The study subjects in Cohort 2 South Africa will be followed until the end of the RV season in 2008 (between 1 August 2008 and 15 September 2008), and the intended duration of the study, per subject, will not exceed a maximum of 24 months. The study subjects in the Cohort in Malawi will be followed until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) and the study duration will not exceed a maximum of 24 months.***

Synopsis (number of subjects) and Section 4.1

~~A minimum of 2,600 subjects will be enrolled in South Africa and a maximum of 3070 subjects will be enrolled in Malawi.~~

~~Enrolment will be terminated when 4,800 subjects have been enrolled.~~

Total target enrolment will be ~~5,670~~ ***4,800*** subjects (~~1,890~~ ***1,600*** subjects in each group).

All enrolled subjects will be followed for efficacy and safety. The subjects in ***Cohort 1 in South Africa*** will be followed for efficacy and safety until one year of age. ***The subjects in Cohort 2 South Africa will be followed for efficacy and safety until the end of the 2008 RV season (between 1 August 2008 and 15 September 2008). All subjects in Malawi will continue efficacy and safety follow-up until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009).***

Section 5.1.2

The parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi, who are interested to continue the participation of their child in the second year follow-up will be presented an ICF supplement to obtain their written informed consent.

An ICF will also be given to the parents/guardians of subjects (irrespective of their decision to let their child/ward participate in the second year follow-up period but for whom HIV test will be performed on the child/ward post cessation of breast feeding) to obtain their consent to record the results of HIV tests conducted post-breast feeding cessation in the CRF when performed.

Section 5.2

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- During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 up until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the ***site*** or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.*** HIV testing performed at hospital admission should be recorded in the CRF.
- National Guidelines ***for the management of HIV infected children*** in South Africa recommend HIV testing 6 weeks after breast feeding cessation ***and the National Guidelines for the management of HIV infected children in Malawi recommends the HIV testing 3 months after breast feeding cessation.*** This testing will be done through the usual clinic/paediatric outpatient system. The results of repeat test after breast feeding ceases should be recorded in the CRF.
- ~~All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF. (Amendment 1: 24 August 2005).~~
- GE surveillance:

  Active surveillance for GE (diarrhoea) will be conducted by the study staff during the entire study period (starting at Dose 1 until Visit 6 ***for subjects in Cohort 1 in South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 in South Africa and the Cohort in Malawi***).

- Collection of stool samples:

  Parents/guardians of all subjects will be instructed to collect stool sample(s) if the subject develops diarrhoea at any time until Visit 6 ***for subjects in Cohort 1 in South Africa, and from the day of Dose 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi.***

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Section 5.4

Table 1 List of study procedures for Cohort 1 and 2 enrolled in South Africa and all subjects enrolled in Malawi

Age	5-10 weeks						
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6	*VISIT 7*
Timing	Day 0	Month 1	Month 2	Month 3	Month 4	1 year of age	*End of 2nd efficacy follow-up period*
Sampling timepoint	**Pre**			**Post vacc 3**			
Informed consent	•						
Informed consent addendum for HIV testing§	•			•			
Supplementary ICF for using results of HIV testing performed after breast feeding cessation						•	
Supplementary ICF for participation in 2nd efficacy follow-up						•	
Medical history	•						
Medical history for HIV	•						
Check of inclusion criteria	•						
Check of exclusion criteria	•						
Check of elimination criteria		•	•	•		•	•
Check of contraindications	•	•	•				
Randomisation	•						
Physical examination	•	#	#	#		#	#
Pre-vaccination body temperature	•	•	•				
Measure/record height and weight	•			•		•	•
Blood sampling							
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects			
For HIV testing, if and when accepted‡	• (3 ml in South Africa and 1 ml in Malawi)			• (3 ml in South Africa and 1 ml in Malawi)			
Confirmatory HIV testing, if required		• (2 ml in South Africa and 1 ml in Malawi)			• (2 ml in South Africa and 1 ml in Malawi)		
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•	•
Study vaccination (HRV or placebo)	•	•	•				
Routine EPI vaccination	•	•	•				
Recording of AEs leading to drop-out	•	•	•	•		•	•

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Age	5-10 weeks						
Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5†	VISIT 6	*VISIT 7*
Timing	Day 0	Month 1	Month 2	Month 3	Month 4	1 year of age	*End of 2nd efficacy follow-up period*
Sampling timepoint	Pre			Post vacc 3			
Return of completed diary cards by parents/guardians		•	•	•		•	•
Diary card transcription		•	•	•		•	•
Recording concomitant medication/vaccination	•	•	•	•		•**	•**
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•	•
Record results of HIV testing		•	•		•		
Inform subjects of HIV result		•	•		•		
Record results of HIV testing after breast feeding ceases						•	•
Study Conclusion						•	•

§During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the ***site*** or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.***

•** Only concomitant medication administered for treatment of GE, AE leading to drop-outs and SAEs will be recorded during this period.

Visit 7 is for subjects in Cohort 2 South Africa and the Cohort in Malawi only.

Table 2 Intervals between study visits for Cohort 2 enrolled in South Africa and all subjects enrolled in Malawi

Interval	Size of interval
Visit 7	***1 August 2008 - 15 September 2008 (end of RV season) for Cohort 2 South Africa and until at least 18 months of age and not more than two years of age (last subject last visit not later than 30 January 2009) for the Cohort in Malawi***

Section 5.5

Visit 6, Follow-up (343-391 days of age)

- ~~Study conclusion.~~
- Record any concomitant~~/intercurrent vaccinations and~~ medications administered ***for the treatment of GE, SAEs and AEs leading to drop-outs*** in the CRF.
- ***The parents/guardians of subjects in Cohort 2 in South Africa and the Cohort in Malawi, who are interested to continue the participation of their child in the second year follow-up will be presented a supplementary ICF to obtain their written informed consent.***

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- ***A supplementary ICF will be presented to the parents/guardians of subjects to obtain their consent to record the results of HIV tests conducted after breast feeding cessation in the CRF when performed.***
- ***A 'GE diary card' will be provided to parents/guardians of all subjects who provide consent to continue participation during the second efficacy follow-up period, and will be used by the study staff during home visits to record information on any GE episodes occurring until Visit 7. The parents/guardians will be instructed to return their completed diary cards to the investigator at the next visit.***
- ***Stool samples should be collected from the subject during each GE episode and returned to the investigator on an ongoing basis. Also refer to instructions in Appendix D. Two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.***
- ***Parents/guardians should contact the study physician or study staff if the subject manifests any of these signs or symptoms and that they perceive as serious.***
- ***Parents/guardians will be reminded to attend the local hospital, close to the site of the clinics for after-hours consultation.***

Visit 7, Follow-up (end of RV season 2008 i.e. between 1 August 2008 and 15 September 2008 for subjects in Cohort 2 South Africa and until at least 18 months of age and not more than two years of age i.e. last subject last visit not later than 30 January 2009 for all subjects in Malawi)
Visit 7 is for subjects in Cohort 2 South Africa and the Cohort in Malawi only.

- ***Physical examination.***
- ***Recording of height and weight.***
- ***Check of elimination criteria.***
- ***Record any concomitant medications administered for the treatment of GE, SAEs and AEs leading to drop-outs in the CRF.***
- ***Recording of SAEs that may have occurred since Visit 6.***
- ***Record results of HIV testing after breast feeding cessation in the CRF if consent to use the results was obtained from the parents/guardiand and if the HIV test was perfomed since the previous visit.***
- ***Collection and verification of the 'GE diary card'. The investigator will verify the diary card and transcribe the information into the appropriate sections of the CRF, in English. The study monitor may help in this translation.***
- ***Return any stool samples.***
- ***Record AEs leading to drop-out in the CRF.***
- ***Study conclusion.***

Section 5.6.2

All stool samples collected during diarrhoea episodes from Visit 1 to Visit ~~6~~ *7* will be processed at the study site or designated laboratory and shipped frozen to GSK Biologicals, Belgium.

HIV assay

- During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with SAE and any HIV testing has not yet been performed, HIV testing and the concerned informed consent will be proposed at the site, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.***

Figure 1 Algorithm for HIV testing in South Africa

Note: DNA testing using PCR as specified in the Figure 1 is applicable to subjects only up to 18 months of age, whose mothers tested positive for HIV or for whom their mother's status was not known but the ELISA was reactive. ELISA tests would be performed on subjects after 18 months of age. As per the South African Guidelines no DNA PCRs will be performed for subjects after 18 months of age.

Table 3 Read-outs

Sampling timepoint			Marker	No. subjects	Marker priority rank
Timing	Month	Visit no			
GE stool analysis					
At all times from Visit 1 until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***			RV antigen	All	None

Section 6.4

Target enrolment will be ~~5,670~~ ***4,800*** subjects (~~1,890~~ ***1,600*** subjects in each group).

Section 6.5

Blinding will be maintained for the whole study period (see Section 10.7 for details on how the individual blinding will be maintained despite statistical analyses before all study data are collected/processed). This will allow unbiased evaluation of the study vaccine.

Section 6.9

Concomitant medication administered for the treatment of a ***SAE and AE**** within the follow-up period for adverse events must be recorded in the CRF 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.

Any investigational medication or vaccine administered throughout the study (from Visit 1 to Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***) must be recorded in the CRF.

Any ARV therapy given throughout the study (from Visit 1 to Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***) must be recorded in the CRF.

Section 8.4

During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi)*** ~~must be recorded in the CRF)~~), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.*** HIV testing performed at hospital admission should be recorded in the CRF.

Section 8.5

All AEs leading to subject withdrawal/drop-out during the period starting at Visit 1 and ending at Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi*** must be recorded in the subject's CRF.

Section 8.6.1

The investigator will make an assessment of the maximum intensity that occurred over the duration of the event for AEs leading to drop-out ~~from Visit 1 to Visit 6~~ and SAEs reported from Visit 1 to Visit 6 ***for subjects in Cohort 1 South Africa, and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi.***

Section 8.7

During the entire study period (from Visit 1 up until Visit 6 ***for subjects in Cohort 1 South Africa and from Visit 1 until Visit 7 for subjects in Cohort 2 South Africa and the Cohort in Malawi***), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed ***at the site*** or, in the case of hospitalisation, at hospital admission if possible. ***For subjects in Cohort 2 South Africa HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics and/or hospitals as indicated per clinical symptoms.***

Section 8.8.2

Study Contact for Reporting SAEs
Refer to the Sponsor Information Sheet
Back-up Study Contact for Reporting SAEs Refer to the Sponsor Information Sheet
GSK Biologicals Clinical Safety Physician Tel: [redacted] Fax [redacted]
Mobile phone for 7/7 day availability: [redacted] (Head Safety Evaluation and Risk Management Paediatrics) Back-up mobile phone contact: [redacted]
24/24 hour and 7/7 day availability

Section 8.12

Treatment of any adverse event ***leading to drop-outs and SAEs*** is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE* and ***SAEs*** should be recorded in the subject's CRF.

Synopsis (secondary endpoints) and Section 10.2

For subjects in Cohort 2 South Africa:

- ***Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system [Ruuska, 1990]) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***
- ***Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.***

Section 10.3

A total of ~~5,670~~ ***4,800*** subjects (~~1,890~~ ***1,600*** subjects in each group) will be enrolled. Allowing for approximately 15% of subjects who may not be evaluable for analyses of

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the primary objective, ~~4,800~~ ***3,960*** evaluable subjects (~~1,600~~ ***1,320*** subjects in each group) are expected to be evaluable for the analysis of the primary objective.

Assuming a ***2%*** incidence of severe RV GE in the placebo group during the observation period, and a 60% vaccine efficacy, the sample size of ~~4,800~~ ***3,960*** evaluable subjects has ~~80%~~ ***84%*** power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95%CI on vaccine efficacy >0%).

~~**Table 5 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 1,600 evaluable subjects, N HRV pooled groups = 3,200 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)**~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6~~		
	~~60%~~	~~70%~~	~~80%~~
~~1%~~	~~60%~~	~~78%~~	~~92%~~
~~1.5%*~~	~~80%~~	~~93%~~	~~98%~~
~~2%~~	~~90%~~	~~98%~~	~~99%~~
~~3 %~~	~~98%~~	~~99%~~	~~100%~~

~~*Anticipated incidence rate~~

Table 5 Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = *1,320* evaluable subjects, N HRV pooled groups = *2,640* evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)

Incidence rate in the placebo	True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6		
	60%*	70%	80%
1%	*50%*	*69%*	*86%*
1.5%	*71%*	*87%*	*97%*
*2%**	*84%*	*95%*	*99%*
3 %	*95%*	*99%*	*99%*

*Anticipated incidence rate

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Amendment 6

~~Table 6 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,600 evaluable subjects, N HRV group = 1,600 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)~~

~~Incidence rate in the placebo~~	~~True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6~~		
	~~60%~~	~~70%~~	~~80%~~
~~1%~~	~~46%~~	~~64%~~	~~82%~~
~~1.5%*~~	~~66%~~	~~84%~~	~~95%~~
~~2%~~	~~80%~~	~~93%~~	~~98%~~
~~3 %~~	~~93%~~	~~99%~~	~~99%~~

~~*Anticipated incidence rate~~

Table 6 Power to detect a statistically significant difference between each HRV group and placebo (N placebo = 1,320 evaluable subjects, N HRV group = 1,320 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation, no adjustment for multiplicity)

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6*		
	60%	*70%*	*80%*
1%	*38%*	*55%*	*73%*
1.5%	*57%*	*76%*	*90%*
*2%**	*71%*	*88%*	*97%*
3 %	*89%*	*97%*	*99%*

Anticipated incidence rate

Estimation of power for the second efficacy period

With respect to the year 2 efficacy follow-up, Table 7 presents the power to detect a statistically significant difference between the pooled HRV groups and placebo group for a range of vaccine efficacy. If the VE is truly 60% and assuming a 2% incidence of severe RV GE in the placebo group, a sample size of 2325 evaluable subjects has 59% power to detect a statistically significant difference between the pooled HRV groups and placebo group (lower limit of the 95% CI on vaccine efficacy >0%).

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Table 7 ***Power to detect a statistically significant difference between the pooled HRV groups and placebo (N placebo = 775 evaluable subjects, N HRV pooled groups = 1550 evaluable subjects, alpha=2.5%, PASS 2000, power for detecting difference between 2 groups, one-sided Chi-square test with continuity correction and arcsine transformation)***

Incidence rate in the placebo	*True Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV strains during the period from Visit 6 up to Visit 7*		
	*60%**	*70%*	*80%*
1%	29%	43%	60%
*2%**	59%	78%	92%
3 %	79%	93%	99%

****Anticipated incidence rate***

Section 10.4

Total vaccinated cohort

- an efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects ~~for whom efficacy follow-up data are available after dose 1 of HRV vaccine or placebo~~.

According-to-protocol (ATP) safety cohort

- who have not received a replacement vial, ***except if the appropriate vaccine was administered in "double-blind replacement"***.

ATP efficacy cohort

- who have entered into the efficacy surveillance period:
  - have follow-up beyond 2 weeks after the last dose of the study vaccination course ***for analysis of the first and combined efficacy follow-up periods.***
  - ***have*** follow-***up beyond the end of the first efficacy follow-up period for analysis of the second efficacy follow-up period.***

Section 10.6

Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. (Amendment 1: 24 August 2005). ***A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.***

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed after subjects have completed Visit 7, and will be presented in an annex report.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 6. However, access to the individual treatment

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decode will be provided to the investigators only after the final analyses of the second efficacy follow-up has been performed.

Section 10.6.2

In addition, vaccine efficacy will be calculated, with their 95% CI, against

- ***severe RV GE caused by the circulating wild-type RV strains, hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE, severe RV GE (G1 and non-G1) for the second and combined efficacy periods and for pooled HRV groups.***
- ***severe RV GE caused by the circulating wild-type RV strains after 3 doses of HRV vaccine versus 2 doses of HRV vaccine for the combined efficacy period.***

Section 10.6.3

The height and weight increase from Visit 1 to Visits 4, 6 and 7 will be summarised by group.

Section 10.7

~~There is no planned interim analysis~~.

An interim analysis on vaccine efficacy against severe RV GE and any RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be descriptive and will not be used to conclude on vaccine efficacy.The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. The interim analysis will be based on the total vaccinated cohort for the subset of subjects with efficacy follow-up 2 weeks beyond study dose 3. The estimated VE against any wild-type RV GE and severe wild-type RV GE will be provided for the pooled HRV groups versus the placebo group. Distribution of RV GE by serotype will also be available although this will not be provided by group.The interim analysis will be dissemintated within GSK and shared with the RVP organization and the investigators.

Table 8 indicates the level of accuracy that can be expected for the interim evaluation of efficacy against severe RV GE.

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Table 8 ***Power at interim analysis to get an exact confidence interval for the vaccine efficacy above 0% for a true VE of 60% and 70%, and for different total number of severe RV GE episodes reported (ratio 2:1 (pooled HRV groups:placebo), alpha=0.1%, PASS 2005)***

Total number of severe RV GE episodes reported in the three groups	*Power*	
	Vaccine efficacy of 60%	*Vaccine efficacy of 70%*
80	*81%*	*98%*
70	*71%*	*96%*
65	*65%*	*94%*
60	*58%*	*90%*
40	*34%*	*70%*
30	*25%*	*54%*
20	*14%*	*32%*
10	*2%*	*6%*

Since the interim analysis will be descriptive and will not be used to conclude on vaccine efficacy, no adjustment on the alpha will be applied for the final analyses of efficacy.

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Appendix C

- Target enrolment will be ~~5,670~~ ***4,800*** eligible subjects.
- ~~Enrolment will continue until a total of ***4,800*** subjects are enrolled in the study. (Amendment 1: 24 August 2005) (Amendment 2: 27 October 2005) (Malawi-specific amendment 4: 15 May 2006) (South Africa-specific Amendment 5: 10 July 2006).~~
- ~~Recruitment will be terminated when 5,670 eligible subjects have been enrolled.~~
- ~~A minimum of 2,600 subjects will be enrolled in South Africa and a maximum of 3070 subjects will be enrolled in Malawi.~~ Enrolment will continue until a total of ~~5670~~ ***4,800*** subjects are enrolled in the study.
- The intended duration of the study ***for subjects in Cohort 1 South Africa***, per subject, will not exceed a maximum of 10 to 11 months. ***The intended duration of the study, per subject, will not exceed a maximum of 24 months for subjects in Cohort 2 South Africa and the Cohort in Malawi.***

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102248 (Rota-037)
Amendment 6

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	Rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Amendment 6
Amendment date:	**2 August 2007**
Approved by: **Director**	[redacted] 06-08-2007 dd-mm-yyyy

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GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-track #
Rota-037 (South Africa)	102248

Date: 18 March 2009

***Concerns:* Amendment 5 and 6 Investigator Signature Page**

Details:

Dr [redacted] signed the correct version of the Investigator Signature page for Amendment 5 that is in the files although the CARS footer is missing.

Doctors [redacted] and [redacted] have all signed the correct version of the Amendment 6 Investigator Signature page although the checksum is missing.

GSM Responsible: [redacted]

Signature: [redacted]

Signature Date: MAR 18 2009

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102248 (Rota-037)
Amendment 6

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Amendment number:	Amendment 6
Amendment date:	**2 August 2007**

Agreed by:
Investigator:

Investigator signature: [redacted]

Date: 1 OCT 2007

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102248 (Rota-037)
Amendment 6

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Amendment number:	Amendment 6
Amendment date:	**2 August 2007**
Agreed by: **Investigator:** **Investigator signature:** **Date:** 2007/09/20	[redacted]

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102248 (Rota-037)
Amendment 6

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Amendment number:	Amendment 6
Amendment date:	**2 August 2007**
Agreed by: **Investigator:** **Investigator signature:** **Date:** 27 SEPT 07.	[redacted]

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102248 (Rota-037)
Amendment 6

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
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Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Amendment 6
Amendment date:	**2 August 2007**

Agreed by:
Investigator: Dr [redacted]

Investigator signature: [redacted]

Date: 20 SEP 2007.

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102248 (Rota-037)
Amendment 6

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

cTrack study number	102248
cTrack abbreviated title	Rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Amendment 6
Amendment date:	2 August 2007

Agreed by:
Investigator:

Investigator signature: [redacted]

Date: 21 Sep 2007

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GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number	102248
eTrack abbreviated title	Rota-037
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Amendment number:	Amendment 6
Amendment date:	**2 August 2007**
Agreed by: **Investigator:**	DR [redacted]
Investigator signature:	[redacted]
Date:	10 JUNE 2008

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102248 (Rota-037) & 111274 (ROTA-037 EXT:Y2)
Administrative Change 2

Protocol Administrative Change Sponsor Signatory Approval

(Administrative Change 2: 30 August 2007)

eTrack study number *and abbreviated title*	102248 (Rota-037) *111274 (ROTA-037 EXT:Y2)* **(Administrative Change 2: 30 August 2007)**
Date of *protocol*	27 April 2005 – Final Protocol
(Administrative Change 2: 30 August 2007)	24 August 2005 – Amendment 1 22 September 2005 – Administrative change 1 27 October 2005 – Amendment 2 22 February 2006 – Malawi-specific Amendment 3 15 May 2006 – Malawi-specific Amendment 4 10 July 2006 – South Africa-specific Amendment 5 2 August 2007 – Amendment 6 **30 August 2007 – Administrative change 2**
Title	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 1: 24 August 2005)
Sponsor signatory:	[redacted] (Amendment 1: 24 August 2005) (Amendment 6: 2 August 2007)
Signature:	[redacted]
Date:	13 NOV 2007

(Administrative Change 2: 30 August 2007)

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GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-track #
Rota 037	111274

Date: 09 November 2007

Details:

This File note serves to document that the Sponsor Signature Sheet that belongs to the Administrative Changes 2 to Am no 6 to the Rota-037 Protocol dated 30AUG2007 has been signed off on 13NOV2007

[redacted]
Clinical Study Coordinator

Signature: [redacted]

Signature Date: 13 NOV 2007

[redacted]
Clinical Development Manager:

Signatu[redacted]

Signature Date: 13 NOV 2007

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-Track #
Rota – 037	102248

Date: 29MAY2008

Details:

This file note serves to document the following:

- Protocol Administrative Change 2, 30AUG2007: The investigators have signed on a protocol agreement version before QC (formatting QC). Even though it's the wrong page signed, the signatures are still valid.
- Protocol South Africa Specific Amendment 5, 10JUL2006: On the approval page of the investigator agreement, the cars footer was missing for the sign off of Dr. [redacted] Even though the cars footer is missing, the investigator signed the final version of the protocol.
- Protocol Malawi Specific Amendment 4, 15MAY2006: On the approval page of the investigator agreement, the cars footer was missing for the sign off of Dr. [redacted] Even though the cars footer is missing, the investigator signed the final version of the protocol.

This file note provides an official record of this process:

File note created by: [redacted] **(GSM)** **Signature:** [redacted]

Signature Date: 30 May 2008

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102248 (Rota-037)
111274 (ROTA-037 EXT:Y2)
Administrative Change 2

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number ***and abbreviated title***	102248 (Rota-037)
	111274 (ROTA-037 EXT:Y2)
Protocol title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. (Amendment 2 : 27 October 2005)
Administrative Change number:	**Administrative Change 2**
Administrative Change date:	**30 August 2007**
Agreed by: **Investigator:** **Investigator signature:**	[redacted]
Date:	19 MAR 08

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102248 (Rota-037)
111274 (ROTA-037 EXT:Y2)
Administrative Change 2

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number *and abbreviated title*	102248 (Rota-037)
	111274 (ROTA-037 EXT:Y2)
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Administrative Change number:	**Administrative Change 2**
Administrative Change date:	**30 August 2007**
Agreed by: Investigator:	Dr [redacted]
Investigator signature:	[redacted]
Date:	17 APR 2008

[redacted]

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other required documents.

Investigator name: [redacted] 06 NOV 2007

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GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment Approval

eTrack study number *and abbreviated title*	102248 (Rota-037)
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Administrative Change number:	**Administrative Change 2**
Administrative Change date:	**30 August 2007**
Agreed by: **Investigator:**	
Investigator signature:	[redacted]
Date:	20/VIAR/2008

CLEARED ON ORIGINAL

[redacted] 20/03/08

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Investigator name: [redacted] Dr [redacted]

04/11/2007

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GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment Approval

eTrack study number *and abbreviated title*	102248 (Rota-037)
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Administrative Change date:	**30 August 2007**
Agreed by: **Investigator:**	DR [redacted]
Investigator signature:	[redacted]
Date:	14 NOV '07

Sample Case Report Form

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CASE REPORT FORM

Centre number |__|__|__|__|__|__|

Subject number |__|__|__|__|__|__|

Treatment number |__|__|__|__|__|

Protocol 102248
(Rota-037)
MODIFICATION 1

A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants in South Africa.

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax [redacted]

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GENERAL INSTRUCTIONS

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

DATES

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example: |0|1| |J|A|N| |2|0|0|5|= 1st January 2005
day month year

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Study Conclusion** form**.**

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ADVERSE EVENT DEFINITIONS

GASTROENTERITIS SYMPTOMS

Vomiting
One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours

Diarrhea
Passage of three or more looser than normal stools (loose or watery stools), within 24 hours

Gastroenteritis Episodes
Diarrhea with or without vomiting.

INTENSITY SYMPTOMS FOR ADVERSE EVENT (AE)

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/a day-care center and would cause the parents/guardians to seek medical advice).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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

OUTCOME

1: Recovered / Resolved
2: Recovering / Resolving: Subject is recovering at the time she/he completes the study or at the time she/he withdraws from study.
3: Not recovered / Not resolved: AE is ongoing at the time the subject completes the study or becomes lost to follow-up; in case of death AEs that are not the cause of death.
4: Recovered with sequelae / Resolved with sequelae
5: Fatal: AE is the cause of death (only applicable for SAE reports)

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life threatening
- results in persistent or significant disability / incapacity
- requires in-patient hospitalization
- prolongation of existing hospitalization
- is a congenital anomaly / birth defect in the offspring of a study subject
- In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

For each serious adverse event, please fill in a **Serious Adverse Event (SAE)** report and fax it to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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104248 (Rota-037)

FLOW SHEET

Age	**5-10 weeks**				
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**1 year of age**
Sampling timepoint	**Pre**			**Post vacc 3**	
Informed consent	●				
Medical history	●				
Check of inclusion criteria	●				
Check of exclusion criteria	●				
Check of elimination criteria		●	●	●	●
Check of contraindications	●	●	●		
Randomisation	●				
Physical examination	●	#	#	#	#
Pre-vaccination body temperature	●	●	●		
Measure/record height and weight	●			●	●
Blood sampling	●* (2 ml) in subset (N=420)			● (3 ml) in all subjects	
Collection of a stool sample if the child is suspected of GE	●	●	●	●	●
Study vaccination (HRV or placebo)	●	●	●		
Routine EPI vaccination	●	●	●		
Recording of AEs leading to drop-out	●	●	●	●	●
Return of completed diary cards by parents/guardians		●	●	●	●
Diary card transcription		●	●	●	●
Recording concomitant medication/vaccination	●	●	●	●	●
Reporting of SAEs occurring throughout the study period, by investigator	●	●	●	●	●
Study Conclusion					●

● is used to indicate a study procedure which requires documentation in the individual eCRF.
* = The blood sample will be collected before administering the dose of vaccine/placebo.
# is used to indicate a study procedure which does not require documentation in the individual eCRF.

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

Intervals between study visits

Interval	**Size of interval**
1 (Visit 1→Visit 2)	30 to 48 days
2 (Visit 2→Visit 3)	30 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days
Visit 5	343-391 days of age

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VISIT 1

DAY 0

(5 - 10 WEEKS OF AGE)

DOSE 1

Informed Consent has to be obtained prior to any study procedure

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102248 (Rota-037)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol analysis.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)

[C] Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.

[D] Administration of immunoglobulins and/or any blood products during the study period.

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

GSK Biologicals' HRV vaccine or its placebo

The following AEs constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any AE:

[A] Hypersensitivity reaction due to the vaccine.

[B] IS.

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

[C] Axillary temperature ≥ 37.5°C or rectal temperature ≥ 38.0°C.

[D] GE within 7 days preceding the study vaccine administration.

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102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__| day month year

DEMOGRAPHICS

Center number: |__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender:
- [M] ☐ Male
- [F] ☐ Female

Race:
- [1] ☐ 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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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 child between, and including, 5 and 10 weeks of age at the time of the first study vaccination.

[3] ☐ Written informed consent obtained from the parent or guardian of the subject

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ Birth weight > 2000 g.

EXCLUSION CRITERIA

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ 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).

[8] ☐ Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.

[9] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)

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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|

EXCLUSION CRITERIA (continuing)

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[10] ☐ History of use of experimental rotavirus vaccine.

[11] ☐ Previous routine vaccination except BCG, HBV and OPV vaccination at birth (should be documented in the eCRF).

[12] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.

[13] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

[14] ☐ History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

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

[16] ☐ Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).

[17] ☐ Previous confirmed occurrence of RV GE.

[18] ☐ A family history of congenital or hereditary immunodeficiency.

[19] ☐ Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.

[20] ☐ History of any neurologic disorders or seizures.

[21] ☐ Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number: |__|__|__|__|

3.

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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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
Skin and subcutaneous tissue	_____	☐	☐
	_____	☐	☐
Musculoskeletal and connective tissue	_____	☐	☐
	_____	☐	☐
Cardiac	_____	☐	☐
	_____	☐	☐
Vascular	_____	☐	☐
Respiratory, thoracic and mediastinal	_____	☐	☐
	_____	☐	☐
Gastrointestinal	_____	☐	☐
	_____	☐	☐
Hepatobiliary	_____	☐	☐
Renal and urinary	_____	☐	☐
Nervous system	_____	☐	☐
Eye	_____	☐	☐
Ear and labyrinth	_____	☐	☐
Endocrine	_____	☐	☐
Metabolism and nutrition	_____	☐	☐
Blood and lymphatic system	_____	☐	☐
Immune system (incl. allergies, autoimmune disorders)	_____	☐	☐
	_____	☐	☐
Infections and infestations	_____	☐	☐
Neoplasms benign, malignant and unspecified (incl. cysts, polyps)	_____	☐	☐
Surgical and medical procedures	_____	☐	☐
	_____	☐	☐
Other	_____	☐	☐
	_____	☐	☐

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

4.

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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE (2 ml for subset only)

Has a blood sample been taken?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

☐ NA

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

DTPw-HB/Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

5.

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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1** **DOSE 1**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__| . |__| °C → Route: [A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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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VISIT 2

MONTH 1

30 ±8 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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

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GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

7.

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GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 1 and Visit 2?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

DTPw-HB/Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

8.

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GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 2** **DOSE 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

9.

CONFIDENTIAL

VISIT 3

MONTH 2

30 ±8 days after Visit 2

DOSE 3

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

10.

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102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 2 and Visit 3?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

DTPw-HB/Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

11.

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GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 3** **DOSE 3**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

12.

CONFIDENTIAL

VISIT 4

MONTH 3

30 ±48 days after Visit 3

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

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GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

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102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

LABORATORY TESTS

BLOOD SAMPLE (3 ml for all subjects)

Has a blood sample been taken for Rota and HIV assay?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

→ Result for HIV Assay: Positive ☐
Negative ☐

☐ No

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 3 and Visit 4?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

14.

CONFIDENTIAL

VISIT 5

1 year of age

343 - 391 days of age

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

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102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

15.

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102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 5**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 4 and Visit 5?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

16.

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GASTROENTERITIS EPISODES

VISIT 1 – VISIT 5

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102248 (Rota-037)

Protocol		GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 5	Subject Number
102248			|__|__|__|__|__|__|

Has any gastroenteritis occurred from Visit 1 until Visit 5?
- ☐ No
- ☐ Yes → Please complete below and next pages if necessary.

Episode N° |__|__|

Treatment:
- ☐ No
- ☐ Yes → if yes,
  - ☐ Oral rehydration therapy
  - ☐ IV rehydration therapy
  - ☐ Oral and IV rehydration therapy
  - ☐ Other, please specify: _____

Dehydration?
- ☐ No
- ☐ Yes → if yes:
  - ☐ 1 - 5 %
  - ☐ ≥ 6 %

Hospitalization?
- ☐ No
- ☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis. A second stool sample can be taken if the first one is insufficient.

Stool collection date and time:

1st Stool: |__|__|__|__|__|__|__|__|__|__|__|__| |__|__|:|__|__| (day month year hours min)

2nd Stool: |__|__|__|__|__|__|__|__|__|__|__|__| |__|__|:|__|__| (day month year hours min)

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature → C**	[A] ☐ Axillary **(recommended)** [O] ☐ Oral [R] ☐ Rectal
|__|__||__|__|__||__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__||__|__|__||__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__||__|__|__||__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__||__|__|__||__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken

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102248 (Rota-037)

Protocol		GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 5	Subject Number
102248			|__|__|__|__|__|

Episode N° |__|__|

Treatment:
- ☐ No
- ☐ Yes → if yes,
  - ☐ Oral rehydration therapy
  - ☐ IV rehydration therapy
  - ☐ Oral and IV rehydration therapy
  - ☐ Other, please specify: _____

Dehydration?
- ☐ No
- ☐ Yes → if yes:
  - ☐ 1 - 5 %
  - ☐ ≥ 6 %

Hospitalization?
- ☐ No
- ☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis. A second stool sample can be taken if the first one is insufficient.

Stool collection date and time:

1st Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

2nd Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature → C	[A] ☐ Axillary **(recommended)** [O] ☐ Oral [R] ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken

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102248 (Rota-037)

Protocol		GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 5	Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment:
- ☐ No
- ☐ Yes → if yes,
  - ☐ Oral rehydration therapy
  - ☐ IV rehydration therapy
  - ☐ Oral and IV rehydration therapy
  - ☐ Other, please specify: _____

Dehydration?
- ☐ No
- ☐ Yes → if yes:
  - ☐ 1 - 5 %
  - ☐ ≥ 6 %

Hospitalization?
- ☐ No
- ☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis. A second stool sample can be taken if the first one is insufficient.

Stool collection date and time:

1st Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

2nd Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. **day month year**	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature → C**	[A] ☐ Axillary **(recommended)** [O] ☐ Oral [R] ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken

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102248 (Rota-037)

Protocol		GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 5	Subject Number
102248			|__|__|__|__|__|

Episode N° |__|__|

Treatment:
- ☐ No
- ☐ Yes → if yes,
  - ☐ Oral rehydration therapy
  - ☐ IV rehydration therapy
  - ☐ Oral and IV rehydration therapy
  - ☐ Other, please specify: _____

Dehydration?
- ☐ No
- ☐ Yes → if yes:
  - ☐ 1 - 5 %
  - ☐ ≥ 6 %

Hospitalization?
- ☐ No
- ☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis. A second stool sample can be taken if the first one is insufficient.

Stool collection date and time:

1st Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

2nd Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. **day month year**	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature → C**	[A] ☐ Axillary **(recommended)** [O] ☐ Oral [R] ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken

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102248 (Rota-037)

Protocol		GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 5	Subject Number
102248			|__|__|__|__|__|

Episode N° |__|__|

Treatment:
- ☐ No
- ☐ Yes → if yes,
  - ☐ Oral rehydration therapy
  - ☐ IV rehydration therapy
  - ☐ Oral and IV rehydration therapy
  - ☐ Other, please specify: _____

Dehydration?
- ☐ No
- ☐ Yes → if yes:
  - ☐ 1 - 5 %
  - ☐ ≥ 6 %

Hospitalization?
- ☐ No
- ☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis. A second stool sample can be taken if the first one is insufficient.

Stool collection date and time:

1st Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

2nd Stool: |__|__| |__|__|__| |__|__|__|__| |__|__| : |__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. **day month year**	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature → C**	[A] ☐ Axillary **(recommended)** [O] ☐ Oral [R] ☐ Rectal
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken

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CONCOMITANT VACCINATION

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

- All vaccines administered in the period beginning at birth and ending at study end should be documented in the eCRF with trade name, route of administration and date(s) of administration.

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102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered since birth (except OPV and DTPw-HB/Hib given at visit 1,2 and 3)?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	Route	Administration date day month year
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
NA	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

22.

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MEDICATION

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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
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject/subject's parents/guardians 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 at Visit 1 and ending at 31 days post last vaccine dose are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.
- Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or placebo are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.
- A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C, oral temperature < 37.5°C or axillary temperature < 37.5°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.
- Concomitant medication administered for the treatment of an AE 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 administered throughout the study (from Visit 1 to Visit 5) must be recorded in the eCRF.

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(@)

Protocol	Book			Subject Number
#				|_|_|_|_|_|_|

MEDICATION

Have any medications/treatments been administered during study period?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or 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					

23.

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NON-SERIOUS ADVERSE EVENTS

TO BE FILLED ONLY IN CASE OF DROP-OUT DUE TO NON-SERIOUS AE

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102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP- OUT

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** report).

Has any **non-serious adverse event (leading to drop-outs)** occurred since Visit 1 until Visit 5?

☐ 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

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102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP OUT (continued)

AE No.	**3**	**4**
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__||__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period (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

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STUDY CONCLUSION

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102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event during the study period?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken during the study?

☐ 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 the **Serious Adverse Event** report as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

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CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete Non-serious Adverse Event section
→ Please specify AE No. |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event.

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [OTH] Other, please specify: _____

→ Who made the decision: [I] ☐ Investigator [S] ☐ Subject / [P] Parents/Guardians

→ Date of last contact: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Was the subject in good condition at date of last contact?

☐ No → Please specify: _____

☐ 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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AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

CASE REPORT FORM

Centre number |__|__|__|__|__|__|

Subject number |__|__|__|__|__|__|

Treatment number |__|__|__|__|__|

Protocol 102248
(Rota-037)

Amendment 1 – Modification 2

A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel:[redacted] Fax [redacted]

AMENDMENT 1 - CONFIDENTIAL

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the Subject Number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.

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.

ERRORS/CORRECTIONS: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialled and dated by the investigator or authorised staff.

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 5|= 1st January 2005
day month year

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Study Conclusion** form**..**

AMENDMENT 1 - CONFIDENTIAL

ADVERSE EVENT DEFINITIONS

GASTROENTERITIS SYMPTOMS

Vomiting
One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours

Diarrhea
Passage of three or more looser than normal stools (loose or watery stools), within 24 hours

Gastroenteritis Episodes
Diarrhea with or without vomiting.

INTENSITY SYMPTOMS FOR ADVERSE EVENT (AE)

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/a day-care center and would cause the parents/guardians to seek medical advice).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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

OUTCOME

1: Recovered / Resolved
2: Recovering / Resolving: Subject is recovering at the time she/he completes the study or at the time she/he withdraws from study.
3: Not recovered / Not resolved: AE is ongoing at the time the subject completes the study or becomes lost to follow-up; in case of death AEs that are not the cause of death.
4: Recovered with sequelae / Resolved with sequelae
5: Fatal: AE is the cause of death (only applicable for SAE reports)

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life threatening
- results in persistent or significant disability / incapacity
- requires in-patient hospitalization
- prolongation of existing hospitalization
- is a congenital anomaly / birth defect in the offspring of a study subject

In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

For each serious adverse event, please fill in a **Serious Adverse Event (SAE)** report and fax it to GSK Biologicals Study Contact for SAE reporting within 24 hours.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline Biologicals

104248 (Rota-037)

FLOW SHEET

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	***VISIT 5†***	**VISIT *6***
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 3.5**	**1 year of age**
Sampling timepoint	**Pre**		***Post vacc 2***	**Post vacc 3**		
Informed consent	•					
Informed consent addendum for HIV testing			•			
Medical history	•					
Medical history for HIV	#		•			
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•		•
Check of contraindications	•	•	•			
Randomisation	•					
Physical examination	•	#	#	#		#
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•			•		•
Blood sampling						
To test anti-rotavirus IgA antibodies	•* (2 ml) in subset (N=***570***)			• (***2*** ml) in all subjects		
For HIV testing			***• (3 ml) in subjects whose parent/ guardian has given consent at Visit 3***	***• (2 ml) in subjects who are HIV positive at Visit 3 and asymptomatic for a confirmatory HIV test***		
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•
Study vaccination (HRV or placebo)	•	•	•			
Routine EPI vaccination	•	•	•			
Recording of AEs leading to drop-out	•	•	•	•		•
Return of completed diary cards by parents/guardians		•	•	•		•
Diary card transcription		•	•	•		•
Recording concomitant medication/vaccination	•	•	•	•		•
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•
Record results of HIV testing			•	•		
Inform subjects of HIV result				•	•	
Record results of HIV testing after breast feeding ceases						•
Study Conclusion						•

†Only in subjects with confirmatory HIV test

• is used to indicate a study procedure which requires documentation in the individual CRF.

* = The blood sample will be collected before administering the dose of vaccine/placebo.

is used to indicate a study procedure which does not require documentation in the individual CRF.

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

Intervals between study visits

Interval	**Size of interval**
1 (Visit 1→Visit 2)	30 to 48 days
2 (Visit 2→Visit 3)	30 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days
4 (Visit 4→Visit 5)	***7 to 48 days***
Visit ***6***	343-391 days of age

AMENDMENT 1 - CONFIDENTIAL

VISIT 1

DAY 0

(5 - 10 WEEKS OF AGE)

DOSE 1

Informed Consent has to be obtained prior to any study procedure

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline Biologicals

102248 (Rota-037)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol analysis.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)

[C] Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.

[D] Administration of immunoglobulins and/or any blood products during the study period.

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

GSK Biologicals' HRV vaccine or its placebo

The following AEs constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any AE:

[A] Hypersensitivity reaction due to the vaccine.

[B] IS.

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

[C] Axillary temperature ≥ 37.5℃ or rectal temperature ≥ 38.0℃.

[D] GE within 7 days preceding the study vaccine administration.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol	Book	Visit	Date of visit	Subject Number
102248		**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

INFORMED CONSENT

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Center number: |__|__|__|__|__|__|

Date of Birth: |__|__| |__|__|__| |__|__|__|__|
day month year

Gender:
- [M] ☐ Male
- [F] ☐ Female

Race:
- [1] ☐ 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

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 child between, and including, 5 and 10 weeks of age at the time of the first study vaccination.

[3] ☐ Written informed consent obtained from the parent or guardian of the subject

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ Birth weight > 2000 g.

EXCLUSION CRITERIA

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ 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).

[8] ☐ Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.

[9] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		VISIT 1		|__|__|__|__|__|

EXCLUSION CRITERIA (continuing)

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[10] ☐ History of use of experimental rotavirus vaccine.

[11] ☐ Previous routine vaccination except BCG, HBV and OPV vaccination at birth (should be documented in the eCRF).

[12] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.

[13] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

[14] ☐ History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

[15] ☐ Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5℃ (99.5℉) / A xillary temperature <37.5℃ (99.5℉) / Rectal temperature <38℃ (100.4℉).) (warrants defe rral of vaccination).

[16] ☐ Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).

[17] ☐ Previous confirmed occurrence of RV GE.

[18] ☐ A family history of congenital or hereditary immunodeficiency.

[19] ☐ Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.

[20] ☐ History of any neurologic disorders or seizures.

[21] ☐ Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number: |__|__|__|__|__|

3.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		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
Skin and subcutaneous tissue	_____	☐	☐
	_____	☐	☐
Musculoskeletal and connective tissue	_____	☐	☐
	_____	☐	☐
Cardiac	_____	☐	☐
	_____	☐	☐
Vascular	_____	☐	☐
Respiratory, thoracic and mediastinal	_____	☐	☐
	_____	☐	☐
Gastrointestinal	_____	☐	☐
	_____	☐	☐
Hepatobiliary	_____	☐	☐
Renal and urinary	_____	☐	☐
Nervous system	_____	☐	☐
Eye	_____	☐	☐
Ear and labyrinth	_____	☐	☐
Endocrine	_____	☐	☐
Metabolism and nutrition	_____	☐	☐
Blood and lymphatic system	_____	☐	☐
Immune system (incl. allergies, autoimmune disorders, HIV positivity of mother or infant)	_____	☐	☐
	_____	☐	☐
Infections and infestations	_____	☐	☐
Neoplasms benign, malignant and unspecified (incl. cysts, polyps)	_____	☐	☐
Surgical and medical procedures	_____	☐	☐
	_____	☐	☐
Other	_____	☐	☐
	_____	☐	☐

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

4.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|__|

LABORATORY TESTS

BLOOD SAMPLE (2 ml for subset only)

Has a blood sample been taken?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__| (day month year)

☐ No

☐ NA

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| (day month year)

☐ No

DTPw-HB/Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| (day month year)

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1** **DOSE 1**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__| . |__| °C → Route: [A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, non serious AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

AMENDMENT 1 - CONFIDENTIAL

VISIT 2
MONTH 1
30 – 48 days after Visit 1

DOSE 2

AMENDMENT 1 - 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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

7.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 1 and Visit 2 ?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

DTPw-HB/Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 2** **DOSE 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, non-serious AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

AMENDMENT 1 - CONFIDENTIAL

VISIT 3
MONTH 2
30 – 48 days after Visit 2
DOSE 3

AMENDMENT 1 - 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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

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AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

MEDICAL HISTORY FOR HIV

Has the subject been exposed to HIV?

☐ Yes → *If consent given for blood sample, please do only perform PCR test.*
☐ No
☐ Unknown

INFORMED CONSENT ADDENDUM FOR HIV TESTING

Has the Informed Consent Addendum for HIV testing been signed at visit 3 or previously due to hospitalization or symptoms indicative of AIDS ?

☐ Yes → _ |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

BLOOD SAMPLE FOR HIV TESTING (3ml)

Was a blood sample taken for the HIV testing at visit 3 or previously due to hospitalization or symptoms indicative of AIDS ?

☐ Yes → |__|__| |__|__|__| |__|__|__|__| *(please fill in only if different from visit date)*
day month year

→Elisa testing result:
- ☐ Negative
- ☐ Positive
- ☐ Unknown
- ☐ Not applicable (subjects exposed to HIV)

→PCR testing result:
- ☐ Negative
- ☐ Positive → Need a confirmatory test at visit 4, if HIV asymptomatic up to visit 4.
- ☐ Unknown

☐ No

11.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 3**		|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 2 and Visit 3?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

DTPw-HB/Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 3** **DOSE 3**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |__|__|__|__|__| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

AMENDMENT 1 - CONFIDENTIAL

VISIT 4

MONTH 3

30 – 48 days after Visit 3

AMENDMENT 1 - 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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

HIV TESTING RESULTS

Please communicate the results of the HIV test at visit 3 to parents/guardians and post-test counselling.

If subject tested HIV positive at visit 3 and is asymptomatic, please perform a confirmatory HIV test at visit 4.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

14.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

LABORATORY TESTS

BLOOD SAMPLE (2 ml for all subjects)

Has a blood sample been taken for Rota assay ?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 3 and Visit 4 ?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 4**		|__|__|__|__|__|

BLOOD SAMPLE FOR HIV CONFIRMATORY TESTING (2ml)

Was a blood sample taken for the confirmatory HIV testing ?

☐ Yes → _ |__|__| |__|__|__| |__|__|__|__| *(please fill in only if different from visit date)*
day month year

→ PCR testing result:

☐ Negative
☐ Positive
☐ Unknown

☐ No
☐ NA

16.

AMENDMENT 1 - CONFIDENTIAL

VISIT 5
7 – 48 days after Visit 4

Only in subjects with confirmatory HIV test

HIV TESTING RESULTS

Please communicate HIV test result from confirmatory test at visit 4 to parents/guardians and post-test counselling.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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.

☐ Visit 5 not applicable (subject did not perform a HIV confirmatory test)
☐ 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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

17.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 5**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Did the subject present any gastroenteritis between visit 4 and visit 5 ?

☐ Yes → Please collect a stool sample and fill in the gastroenteritis episode section.
☐ No

18.

AMENDMENT 1 - CONFIDENTIAL

VISIT 6

1 year of age

343 – 391 days of age

AMENDMENT 1 - 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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 6**		|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 6 ?

☐ 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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

19.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 6**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode since last visit and Visit 6 ?

☐ No

☐ Yes → please collect a stool sample and fill in the **Gastroenteritis episodes section.**

HIV REPEAT TEST

Was a blood sample taken after breast feeding cessation (subject HIV exposed but PCR negative at visit 3) ?

☐ Yes → _ |__|__| |__|__|__| |__|__|__|__| *(please fill in only if different from visit date)*
day month year

→ HIV testing result (PCR) :

☐ Negative
☐ Positive
☐ Unknown
☐ NA

☐ No

☐ NA

20.

AMENDMENT 1 - CONFIDENTIAL

GASTROENTERITIS EPISODES

VISIT 1 – VISIT 6

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|

Has any gastroenteritis occurred from Visit 1 until Visit 6 ?

☐ No
☐ Yes → Please complete below and next pages if necessary.

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol			Subject Number
102248	**GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6**		|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: ☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

The first and last date to be considered is the first and last date with at least 3 looser than normal stools. day month year	Number of looser than normal stools per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

AMENDMENT 1 - CONFIDENTIAL

CONCOMITANT VACCINATION

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

- All vaccines administered in the period beginning at birth and ending at study end should be documented in the eCRF with trade name, route of administration and date(s) of administration.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered since birth (except OPV and DTPw-HB/Hib given at visit 1,2 and 3)?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	Route	Administration date day month year
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
NA	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

AMENDMENT 1 - CONFIDENTIAL

MEDICATION

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline Biologicals

- Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject/subject's parents/guardians 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 at Visit 1 and ending at 31 days post last vaccine dose are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.
- Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or placebo are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.
- A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C, oral temperature < 37.5°C or axillary temperature < 37.5°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.
- Concomitant medication administered for the treatment of an AE 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 administered throughout the study (from Visit 1 to Visit 5) must be recorded in the eCRF.

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol	Book			Subject Number
102248				|_|_|_|_|_|_|

MEDICATION

Have any medications/treatments been administered during study period?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or 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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AMENDMENT 1 - CONFIDENTIAL

NON-SERIOUS ADVERSE EVENTS

TO BE FILLED ONLY IN CASE OF DROP-OUT DUE TO NON-SERIOUS AE

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP- OUT

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** report).

Has any **non-serious adverse event (leading to drop-outs)** occurred since Visit 1 until Visit 6 ?

☐ 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

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP OUT (continued)

AE No.	3	4
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__||__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period (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

AMENDMENT 1 - CONFIDENTIAL

STUDY CONCLUSION

AMENDMENT 1 - CONFIDENTIAL

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event during the study period ?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken during the study?

☐ 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 the **Serious Adverse Event** report as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

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Protocol				Subject Number
102248				|__|__|__|__|__|

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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete Non-serious Adverse Event section
→ Please specify AE No. |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event.

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [OTH] Other, please specify: _____

→ Who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

→ Date of last contact: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Was the subject in good condition at date of last contact?

☐ No → Please specify: _____

☐ 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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AMENDMENT 4

GlaxoSmithKline

CASE REPORT FORM

Centre number |__|__|__|__|__|__|

Subject number |__|__|__|__|__|__|

Treatment number |__|__|__|__|__|

Protocol 102248
(Rota-037)
Amendment 4

A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax [redacted]

Confidential - CRF version 12.2 – August 18, 2006

AMENDMENT 4

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the Subject Number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.

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.

Please use missing confirmed "MC" to document that the data is missing.

ERRORS/CORRECTIONS: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialled and dated by the investigator or authorised staff.

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 5| = 1st January 2005
day month year

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Study Conclusion** form**..**

AMENDMENT 4

ADVERSE EVENT DEFINITIONS

GASTROENTERITIS SYMPTOMS

Vomiting
One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours

Diarrhea
Passage of three or more looser than normal stools (loose or watery stools), within 24 hours

Gastroenteritis Episodes
Diarrhea with or without vomiting.

INTENSITY SYMPTOMS FOR ADVERSE EVENT (AE)

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/a day-care center and would cause the parents/guardians to seek medical advice).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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

OUTCOME

1: Recovered / Resolved
2: Recovering / Resolving: Subject is recovering at the time she/he completes the study or at the time she/he withdraws from study.
3: Not recovered / Not resolved: AE is ongoing at the time the subject completes the study or becomes lost to follow-up; in case of death AEs that are not the cause of death.
4: Recovered with sequelae / Resolved with sequelae
5: Fatal: AE is the cause of death (only applicable for SAE reports)

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life threatening
- results in persistent or significant disability / incapacity
- requires in-patient hospitalization
- prolongation of existing hospitalization
- is a congenital anomaly / birth defect in the offspring of a study subject

In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

For each serious adverse event, please fill in a **Serious Adverse Event (SAE)** report and fax it to GSK Biologicals Study Contact for SAE reporting within 24 hours.

AMENDMENT 4

GlaxoSmithKline Biologicals

102248 (Rota-037)

FLOW SHEET

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	***VISIT 5†***	**VISIT *6***
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**1 year of age**
Sampling timepoint	**Pre**			**Post vacc 3**		
Informed consent	•					
Informed consent addendum for HIV testing	•			•		
Medical history	•					
Medical history for HIV	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•		•
Check of contraindications	•	•	•			
Randomisation	•					
Physical examination	•	#	#	#		#
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•			•		•
Blood sampling						
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects		
For HIV testing, ***if and when accepted‡***	•			•		
Confirmatory HIV testing, if required		•			•	
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•
Study vaccination (HRV or placebo)	•	•	•			
Routine EPI vaccination	•	•	•			
Recording of AEs leading to drop-out	•	•	•	•		•
Return of completed diary cards by parents/guardians		•	•	•		•
Diary card transcription		•	•	•		•
Recording concomitant medication/vaccination	•	•	•	•		•
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•
Record results of HIV testing		•	•		•	
Inform subjects of HIV result		•	•		•	
Record results of HIV testing after breast feeding ceases						•
Study Conclusion						•

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries

† ***Visit 5 will take place 21-48 days after Visit 4 o***nly in subjects ***needing a*** confirmatory HIV test

• is used to indicate a study procedure which requires documentation in the individual CRF.

* = The blood sample will be collected before administering the dose of vaccine/placebo.

‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit

is used to indicate a study procedure which does not require documentation in the individual CRF.

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

Intervals between study visits

Interval	Size of interval
1 (Visit 1→Visit 2)	28 to 48 days
2 (Visit 2→Visit 3)	28 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days
*4 (*Visit 4→*Visit 5)*	21 to 48 days
Visit *6*	343-391 days of age

AMENDMENT 4

VISIT 1
DAY 0
(5 - 10 WEEKS OF AGE)
DOSE 1

Informed Consent has to be obtained prior to any study procedure

REMINDERS

HIV TESTING

Offer HIV pre-tests counselling and HIV informed consent to all subjects..

AMENDMENT 4

GlaxoSmithKline Biologicals

102248 (Rota-037)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol analysis.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)

[C] Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.

[D] Administration of immunoglobulins and/or any blood products during the study period.

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

GSK Biologicals' HRV vaccine or its placebo

The following AEs constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any AE:

[A] Hypersensitivity reaction due to the vaccine.

[B] IS.

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

[C] Axillary temperature ≥ 37.5℃ or rectal temperature ≥ 38.0℃.

[D] GE within 7 days preceding the study vaccine administration.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**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 parent or the guardian give their permission that the samples from their child are stored for up to 15 years for the purpose of further testing for the disease and vaccine under study or for quality assurance of laboratory tests, excluding genetic research?

☐ Yes

☐ No

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.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 child between, and including, 5 and 10 weeks of age at the time of the first study vaccination.

[3] ☐ Written informed consent obtained from the parent or guardian of the subject

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

EXCLUSION CRITERIA

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] * ☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ 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).

[8] ☐ Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.

[9] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)

**** criterion 5 is not applicable for amendment 4.***

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|

EXCLUSION CRITERIA (continuing)

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[10] ☐ History of use of experimental rotavirus vaccine.

[11] ☐ Previous routine vaccination except BCG, HBV and OPV vaccination at birth (should be documented in the eCRF).

[12] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.

[13] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

[14] ☐ History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

[15] ☐ Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness, i.e. Oral temperature <37.5℃ (99.5℉) / Axillary temperature <37.5℃ (99.5℉) / Rectal temperature <38℃ (100.4℉).) (warrants deferral of vaccination).

[16] ☐ Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).

[17] ☐ Previous confirmed occurrence of RV GE.

[18] ☐ A family history of congenital or hereditary immunodeficiency.

[19] ☐ Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.

[20] ☐ History of any neurologic disorders or seizures.

[21] ☐ Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number: |__|__|__|__|__|

3.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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
Skin and subcutaneous tissue	_____	☐	☐
	_____	☐	☐
Musculoskeletal and connective tissue	_____	☐	☐
	_____	☐	☐
Cardiac	_____	☐	☐
	_____	☐	☐
Vascular	_____	☐	☐
Respiratory, thoracic and mediastinal	_____	☐	☐
	_____	☐	☐
Gastrointestinal	_____	☐	☐
	_____	☐	☐
Hepatobiliary	_____	☐	☐
Renal and urinary	_____	☐	☐
Nervous system	_____	☐	☐
Eye	_____	☐	☐
Ear and labyrinth	_____	☐	☐
Endocrine	_____	☐	☐
Metabolism and nutrition	_____	☐	☐
Blood and lymphatic system	_____	☐	☐
Immune system (incl. allergies, autoimmune disorders)	_____	☐	☐
	_____	☐	☐
Infections and infestations	_____	☐	☐
Neoplasms benign, malignant and unspecified (incl. cysts, polyps)	_____	☐	☐
Surgical and medical procedures	_____	☐	☐
	_____	☐	☐
Other	_____	☐	☐
	_____	☐	☐

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

4.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|__|

MEDICAL HISTORY FOR HIV

Has the subject been exposed to HIV?

☐ Yes
☐ No
☐ Unknown

HIV TEST **(HIV testing should be proposed to all subjects at Visit 1)**

Was a HIV test performed at Visit 1 ?

☐ Yes → Please complete the specific HIV section.
☐ No

LABORATORY TESTS

BLOOD SAMPLE **(2 ml in South Africa and 1 ml in Malawi for subset only)**

Has a blood sample been taken?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No
☐ NA (for subjects not part of the immuno subset)

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

DTPw-HB vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

5.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1** **DOSE 1**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Pre-Vaccination temperature: \|__\|__\| . \|__\| °C → Route: [A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |___| [W] ☐ Wrong vial number → |__|__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, non serious AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

AMENDMENT 4

VISIT 2
MONTH 1
28 – 48 days after Visit 1

DOSE 2

AMENDMENT 4

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

HIV TESTING RESULTS

Please communicate the results of the HIV test to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

7.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 1 and Visit 2 ?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis episode section.

HIV TEST

(HIV testing should be proposed if a child develops symptoms indicative of AIDS (WHO interim stage III or IV) or has to be hospitalized with SAE, and HIV testing has not yet been performed.)
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.

☐ No

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__\|__\| |__\|__\|__\|__\| |__\|__\|__\|__\| day month year

☐ No

DTPw-HB vaccination

☐ Yes → Administration date if different from visit date: |__\|__\| |__\|__\|__\|__\| |__\|__\|__\|__\| day month year

☐ No

Hib vaccination

☐ Yes → Administration date if different from visit date: |__\|__\| |__\|__\|__\|__\| |__\|__\|__\|__\| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

8.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 2** **DOSE 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Pre-Vaccination temperature: \|__\|__\|. \|__\|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	Side / Site Route
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |___| [W] ☐ Wrong vial number → |__|__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, non-serious AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report.

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.

AMENDMENT 4

VISIT 3
MONTH 2
28 – 48 days after Visit 2
DOSE 3

AMENDMENT 4

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

HIV TESTING RESULTS

Please communicate the results of the HIV test to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

10.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 2 and Visit 3?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis episode section.

HIV TEST

(HIV testing should be proposed if a child develops symptoms indicative of AIDS (WHO interim stage III or IV) or has to be hospitalized with SAE, and HIV testing has not yet been performed.)
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.

☐ No

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

DTPw-HB vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

11.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 3** **DOSE 3**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Pre-Vaccination temperature: \|__\|__\|. \|__\|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |___| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

12.

AMENDMENT 4

VISIT 4
MONTH 3
30 – 48 days after Visit 3

AMENDMENT 4

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

HIV TESTING RESULTS

Please communicate the results of the HIV test to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed.
If HIV not yet performed, offer HIV pre test counselling and HIV informed consent.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

13.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__|.|__| kg

LABORATORY TESTS

BLOOD SAMPLE (2 ml for all subjects in South Africa and 1ml for all subjects in Malawi)

Has a blood sample been taken for Rota assay ?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 3 and Visit 4 ?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis section.

HIV TEST

(HIV testing should be proposed to all subjects who were not tested previously).
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.
☐ No

14.

AMENDMENT 4

VISIT 5
21 – 48 days after Visit 4

Only in subjects with HIV test at visit 4.

HIV TESTING RESULTS

Please communicate HIV test result from test done at visit 4 to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed and plan a contact to inform the parents/guardians about the results.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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.

☐ Visit 5 not applicable (subject did not perform a HIV test at visit 4)
☐ 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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

15.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 5**	|__|__| |__|__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Did the subject present any gastroenteritis between visit 4 and visit 5 ?

☐ Yes → Please ensure a stool sample was collected.
→ Please fill in the gastroenteritis episode section.

☐ No

16.

AMENDMENT 4

VISIT 6

1 year of age

343 – 391 days of age

AMENDMENT 4

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

HIV TEST

Offer a HIV pre-test counselling and the HIV informed consent if a HIV test is proposed between visit 4 and visit 6.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 6**		|__|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 6 ?

☐ 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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

17.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 6**	|__|__| |__|__|__| |__|__|__|__| (day month year)	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode since last visit and Visit 6 ?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis episode section.

HIV TEST

(HIV testing should be proposed if a child develops symptoms indicative of AIDS (WHO interim stage III or IV) or has to be hospitalized with SAE, and HIV testing has not yet been performed.)
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.

☐ No

HIV REPEAT TEST

Was a blood sample taken after breast feeding cessation (repeat test for subjects HIV negative by PCR) ?

☐ Yes → |__|__| |__|__|__| |__|__|__|__| (day month year) *(please fill in only if different from visit date)*

→ HIV testing result (PCR) :

☐ Negative
☐ Positive
☐ Unknown

☐ No

☐ NA

18.

AMENDMENT 4

GASTROENTERITIS EPISODES

VISIT 1 – VISIT 6

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Has any gastroenteritis occurred from Visit 1 until Visit 6 ?
☐ No
☐ Yes → Please complete below and next pages if necessary.

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

19.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

20.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

21.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

22.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_ _ _ _ _ _|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_ _||_ _ _||_ _ _ _|	|_ _|	|_ _|	|_ _|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

24.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

25.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

26.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

28.

AMENDMENT 4

HIV SECTION

REMINDERS

- HIV pre-test counselling and HIV ICF must be offered before any HIV procedure.
- HIV post-test counselling must be offered to all subjects who agreed to a HIV testing.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|

Did the subject have any HIV test performed during the study period ?

☐ Yes → please continue filling the sections here below.
☐ No → please ignore the following questions.

INITIAL HIV TEST

Was a HIV informed consent signed ?

☐ Yes → please indicate the date at which the ICF was signed : |__|__| |__|__|__| |__|__|__|__|
day month year

→ please continue filling the sections here below.

☐ No (please do not record any HIV results in the CRF)

Was a blood sample taken for the initial HIV testing ?

☐ Yes → please specify the date at blood sample collection : |__|__| |__|__|__| |__|__|__|__|
day month year

→ please record result here below :

HIV Elisa/Rapid test

☐ Negative
☐ Positive
☐ Unknown
☐ Not done
☐ NA → only for subjects whose mothers are known to be HIV +

PCR test

☐ Negative
☐ Positive
☐ Unknown
☐ Not done
☐ NA → if Elisa/Rapid test negative

☐ No

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

INITIAL HIV TEST (continued)

Was the initial HIV test result communicated to the parent ?

☐ Yes → please specify the date at which the result was communicated |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No → please specify reason :
- ☐ Subject lost to follow-up
- ☐ Subjects parents/guardians refuse to receive test result
- ☐ Others : _____

Is a confirmatory HIV test required ?

Yes → please continue filling the information here below.
No → please ignore the following question.

CONFIRMATORY HIV TEST

Was a blood sample taken for the HIV confirmatory test :

☐ Yes → please specify date of blood sample collection : |__|__| |__|__|__| |__|__|__|__|
day month year

→ please record result here below :
- ☐ Negative
- ☐ Positive
- ☐ Unknown

☐ No → please specify reason :
- ☐ Subject lost to follow-up
- ☐ Subjects parents/guardians refuse confirmatory test
- ☐ Others : _____

Was the HIV confirmatory test result communicated to the parent ?

☐ Yes → please specify the date at which the result was communicated |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No → please specify reason :
- ☐ Subject lost to follow-up
- ☐ Subjects parents/guardians refuse to receive test result
- ☐ Others : _____

AMENDMENT 4

CONCOMITANT VACCINATION

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

- All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF with trade name, route of administration and date(s) of administration.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered since birth (except OPV and DTPw-HB/Hib given at visit 1,2 and 3)?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	Route	Administration date day month year
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
NA	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

AMENDMENT 4

MEDICATION

AMENDMENT 4

GlaxoSmithKline Biologicals

- Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject/subject's parents/guardians 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 at Visit 1 and ending at 31 days post last vaccine dose are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.
- Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or placebo are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.
- A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C, oral temperature < 37.5°C or axillary temperature < 37.5°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the CRF 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 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 administered throughout the study (from Visit 1 to Visit 6) must be recorded in the CRF.
- Any ARV therapy given throughout the study (from Visit 1 to Visit 6) must be recorded in the CRF.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	Book			Subject Number
102248				|__|__|__|__|__|__|

MEDICATION

Have any medications/treatments been administered during the timeframe as specified in the Protocol ?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick box if continuing at end of study (day month year)	
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|____| End: |__|__|____|	☐
For GSK					

32.

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol	Book			Subject Number
102248				|__|__|__|__|__|__|

MEDICATION (continued)

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					

AMENDMENT 4

NON-SERIOUS ADVERSE EVENTS

TO BE FILLED ONLY IN CASE OF DROP-OUT DUE TO NON-SERIOUS AE

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP- OUT

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** report).

Has any **non-serious adverse event (leading to drop-outs)** occurred since Visit 1 until Visit 6 ?

☐ 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

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP OUT (continued)

AE No.	**3**	**4**
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period (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

AMENDMENT 4

STUDY CONCLUSION

AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event during the study period ?

☐ No ☐ Yes → Specify total number of SAE's: |__|__|

STATUS OF TREATMENT BLIND

Was the treatment blind broken during the study?

☐ 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 the **Serious Adverse Event** report as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

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AMENDMENT 4

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete Non-serious Adverse Event section
→ Please specify AE No. |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event.

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [OTH] Other, please specify: _____

→ Who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

→ Date of last contact: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Was the subject in good condition at date of last contact?

☐ No → Please specify: _____

☐ 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: _____

37.

AMENDMENT 5

GlaxoSmithKline

CASE REPORT FORM

Centre number |__|__|__|__|__|__|

Subject number |__|__|__|__|__|__|

Treatment number |__|__|__|__|__|

Protocol 102248
(Rota-037)
Amendment 5

A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel:[redacted] Fax[redacted]

AMENDMENT 5

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the Subject Number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.

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.

Please use missing confirmed "MC" to document that the data is missing.

ERRORS/CORRECTIONS: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialled and dated by the investigator or authorised staff.

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 5| = 1st January 2005
day month year

The **Medication**, the **Concomitant Vaccination** and the **Non-Serious Adverse Events** sections as well as possible **Serious Adverse Event** report(s) must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Study Conclusion** form**..**

AMENDMENT 5

ADVERSE EVENT DEFINITIONS

GASTROENTERITIS SYMPTOMS

Vomiting
One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours

Diarrhea
Passage of three or more looser than normal stools (loose or watery stools), within 24 hours

Gastroenteritis Episodes
Diarrhea with or without vomiting.

INTENSITY SYMPTOMS FOR ADVERSE EVENT (AE)

1: Mild: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Moderate: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: Severe: An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/a day-care center and would cause the parents/guardians to seek medical advice).

CAUSALITY / RELATIONSHIP TO INVESTIGATIONAL PRODUCTS

Is there a reasonable possibility that the AE may have been caused by the investigational product?

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

OUTCOME

1: Recovered / Resolved
2: Recovering / Resolving: Subject is recovering at the time she/he completes the study or at the time she/he withdraws from study.
3: Not recovered / Not resolved: AE is ongoing at the time the subject completes the study or becomes lost to follow-up; in case of death AEs that are not the cause of death.
4: Recovered with sequelae / Resolved with sequelae
5: Fatal: AE is the cause of death (only applicable for SAE reports)

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life threatening
- results in persistent or significant disability / incapacity
- requires in-patient hospitalization
- prolongation of existing hospitalization
- is a congenital anomaly / birth defect in the offspring of a study subject

In addition, important medical events that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

For each serious adverse event, please fill in a **Serious Adverse Event (SAE)** report and fax it to GSK Biologicals Study Contact for SAE reporting within 24 hours.

AMENDMENT 5

GlaxoSmithKline Biologicals

102248 (Rota-037)

FLOW SHEET

Age	**5-10 weeks**					
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5†**	**VISIT 6**
Timing	**Day 0**	**Month 1**	**Month 2**	**Month 3**	**Month *4***	**1 year of age**
Sampling timepoint	**Pre**			**Post vacc 3**		
Informed consent	•					
Informed consent addendum for HIV testing*†*	•			•		
Medical history	•					
Medical history for HIV	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•		•
Check of contraindications	•	•	•			
Randomisation	•					
Physical examination	•	#	#	#		#
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•			•		•
Blood sampling						
To test anti-rotavirus IgA antibodies	•* (2 ml in South Africa and 1 ml in Malawi) in subset (N=570)			• (2 ml in South Africa and 1 ml in Malawi) in all subjects		
For HIV testing, ***if and when accepted‡***	***• (3 ml in South Africa and 1 ml in Malawi)***			***• (3 ml in South Africa and 1 ml in Malawi)***		
Confirmatory HIV testing, if required		***• (2 ml in South Africa and 1 ml in Malawi)***			***• (2 ml in South Africa and 1 ml in Malawi)***	
Collection of a stool sample if the child is suspected of GE	•	•	•	•		•
Study vaccination (HRV or placebo)	•	•	•			
Routine EPI vaccination	•	•	•			
Recording of AEs leading to drop-out	•	•	•	•		•
Return of completed diary cards by parents/guardians		•	•	•		•
Diary card transcription		•	•	•		•
Recording concomitant medication/vaccination	•	•	•	•		•
Reporting of SAEs occurring throughout the study period, by investigator	•	•	•	•		•
Record results of HIV testing		•	•		•	
Inform subjects of HIV result		•	•		•	
Record results of HIV testing after breast feeding ceases						•
Study Conclusion						•

AMENDMENT 5

GlaxoSmithKline Biologicals

102248 (Rota-037)

FLOW SHEET

Notes

The volumes of the blood samples in two countries are different as a result of the different laboratory requirements in the countries
†***Visit 5 will take place 21-48 days after Visit 4 o***nly in subjects ***who had an initial HIV test at Visit 4***
• is used to indicate a study procedure which requires documentation in the individual CRF.
* = The blood sample will be collected before administering the dose of vaccine/placebo.
‡Testing for HIV should be proposed and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV should be offered at Visit 4. The blood sample for the confirmatory test if required should be obtained at the following visit.
†During the entire study period (from Visit 1 up until Visit 6), if a child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible. HIV testing performed at hospital admission should be recorded in the CRF.
is used to indicate a study procedure which does not require documentation in the individual CRF.

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

Intervals between study visits *for cohort 2 enrolled in South Africa and all subjects enrolled in Malawi*

Interval	Size of interval
1 (Visit 1→Visit 2)	28 to 48 days
2 (Visit 2→Visit 3)	28 to 48 days
3 (Visit 3→Visit 4)	30 to 48 days
4 (Visit 4→Visit 5)	21 to 48 days
Visit 6	343-391 days of age

AMENDMENT 5

VISIT 1
DAY 0
(5 - 10 WEEKS OF AGE)
DOSE 1

Informed Consent has to be obtained prior to any study procedure

REMINDERS

HIV TESTING

Offer HIV pre-tests counselling and HIV informed consent to all subjects..

AMENDMENT 5

GlaxoSmithKline Biologicals

102248 (Rota-037)

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each visit subsequent to the first visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the according-to-protocol analysis.

[A] Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) during the study period.

[B] Chronic administration (defined as more than 14 days) of immunosuppressants during the study period. (Topical steroids are allowed.)

[C] Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.

[D] Administration of immunoglobulins and/or any blood products during the study period.

CONTRAINDICATIONS TO SUBSEQUENT VACCINATION

GSK Biologicals' HRV vaccine or its placebo

The following AEs constitute absolute contraindications to further administration of HRV vaccine or placebo; if any of these AEs occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any AE:

[A] Hypersensitivity reaction due to the vaccine.

[B] IS.

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

[C] Axillary temperature ≥ 37.5℃ or rectal temperature ≥ 38.0℃.

[D] GE within 7 days preceding the study vaccine administration.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**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 parent or the guardian give their permission that the samples from their child are stored for up to 15 years for the purpose of further testing for the disease and vaccine under study or for quality assurance of laboratory tests, excluding genetic research?

☐ Yes

☐ No

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

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 child between, and including, 5 and 10 weeks of age at the time of the first study vaccination.

[3] ☐ Written informed consent obtained from the parent or guardian of the subject who is of legal age (i.e. parent/guardian should be 18 years or older).

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ In South Africa, birth weight > 2000 g or if weight unknown, gestation period > 36 weeks.

EXCLUSION CRITERIA

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.

[7] ☐ 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).

[8] ☐ Planned administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccine(s) and ending 14 days after.

[9] ☐ Chronic administration (defined as more than 14 days) of immunosuppressants since birth. (Topical steroids are allowed.)

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|__|

EXCLUSION CRITERIA (continuing)

Tick (✓) the box corresponding to any of the exclusion criteria that disqualified the subject from entry.

[10] ☐ History of use of experimental rotavirus vaccine.

[11] ☐ Previous routine vaccination except BCG, HBV and OPV vaccination at birth (should be documented in the eCRF).

[12] ☐ Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the gastrointestinal tract, intussusception or other medical condition determined to be serious by the investigator.

[13] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

[14] ☐ History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.

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

[16] ☐ Gastroenteritis within 7 days preceding the first study vaccine administration (warrants deferral of the vaccination).

[17] ☐ Previous confirmed occurrence of RV GE.

[18] ☐ A family history of congenital or hereditary immunodeficiency.

[19] ☐ Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.

[20] ☐ History of any neurologic disorders or seizures.

[21] ☐ Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

RANDOMISATION / TREATMENT ALLOCATION

Record treatment number: |__|__|__|__|__|

3.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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
Skin and subcutaneous tissue	_____	☐	☐
	_____	☐	☐
Musculoskeletal and connective tissue	_____	☐	☐
	_____	☐	☐
Cardiac	_____	☐	☐
	_____	☐	☐
Vascular	_____	☐	☐
Respiratory, thoracic and mediastinal	_____	☐	☐
	_____	☐	☐
Gastrointestinal	_____	☐	☐
	_____	☐	☐
Hepatobiliary	_____	☐	☐
Renal and urinary	_____	☐	☐
Nervous system	_____	☐	☐
Eye	_____	☐	☐
Ear and labyrinth	_____	☐	☐
Endocrine	_____	☐	☐
Metabolism and nutrition	_____	☐	☐
Blood and lymphatic system	_____	☐	☐
Immune system (incl. allergies, autoimmune disorders)	_____	☐	☐
	_____	☐	☐
Infections and infestations	_____	☐	☐
Neoplasms benign, malignant and unspecified (incl. cysts, polyps)	_____	☐	☐
Surgical and medical procedures	_____	☐	☐
	_____	☐	☐
Other	_____	☐	☐
	_____	☐	☐

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

4.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1**		|__|__|__|__|__|__|

MEDICAL HISTORY FOR HIV

Has the subject been exposed to HIV?

☐ Yes
☐ No
☐ Unknown

HIV TEST **(HIV testing should be proposed to all subjects at Visit 1)**

Was a HIV test performed at Visit 1 ?

☐ Yes → Please complete the specific HIV section.
☐ No

LABORATORY TESTS

BLOOD SAMPLE **(2 ml in South Africa and 1 ml in Malawi for subset only)**

Has a blood sample been taken?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No
☐ NA (for subjects not part of the immuno subset)

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

DTPw-HB vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

Hib vaccination

☐ Yes → Administration date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

5.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 1** **DOSE 1**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__| . |__| °C → Route: [A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |___| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, non serious AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

AMENDMENT 5

VISIT 2
MONTH 1
28 – 48 days after Visit 1

DOSE 2

AMENDMENT 5

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

HIV TESTING RESULTS

Please communicate the results of the HIV test to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

7.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 2**	|__|__||__|__|__||__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 1 and Visit 2 ?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis episode section.

HIV TEST

(HIV testing should be proposed if a child develops symptoms indicative of AIDS (WHO interim stage III or IV) or has to be hospitalized with SAE, and HIV testing has not yet been performed.)
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.

☐ No

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year

☐ No

DTPw-HB vaccination

☐ Yes → Administration date if different from visit date: |__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year

☐ No

Hib vaccination

☐ Yes → Administration date if different from visit date: |__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

8.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 2** **DOSE 2**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Pre-Vaccination temperature: \|__\|__\|. \|__\|°C → Route:
[A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |___| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. \|__\|__\|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, non-serious AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report.

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.

AMENDMENT 5

VISIT 3
MONTH 2
28 – 48 days after Visit 2
DOSE 3

AMENDMENT 5

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

Before any vaccine administration, please review the **Contraindications** as specified in the Protocol.

HIV TESTING RESULTS

Please communicate the results of the HIV test to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

10.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 3**	|__|__||__|__|__||__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 2 and Visit 3?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis episode section.

HIV TEST

(HIV testing should be proposed if a child develops symptoms indicative of AIDS (WHO interim stage III or IV) or has to be hospitalized with SAE, and HIV testing has not yet been performed.)
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.

☐ No

ROUTINE VACCINE ADMINISTRATION

OPV

☐ Yes → Administration date if different from visit date: |__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year

☐ No

DTPw-HB vaccination

☐ Yes → Administration date if different from visit date: |__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year

☐ No

Hib vaccination

☐ Yes → Administration date if different from visit date: |__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year

☐ No

If *Yes* is ticked, the above vaccines are not to be reported again in the **Concomitant Vaccination** section at the end of the CRF.

Any other vaccines administered during the study period are to be recorded in the **Concomitant Vaccination** section at the end of the CRF.

11.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 3** **DOSE 3**		|__|__|__|__|__|__|

VACCINE ADMINISTRATION

Date (fill in only if different from visit date) : |__|__| |__|__|__| |__|__|__|__|
day month year

Pre-Vaccination temperature: |__|__|. |__| °C → Route: [A] ☐ Axillary(recommended)
[O] ☐ Oral
[R] ☐ Rectal

VACCINE ADMINISTRATION *(only one box must be ticked by vaccine)*	**Side / Site Route**
[S] ☐ **HRV Vaccine or its placebo** [R] ☐ Replacement vial → |___| [W] ☐ Wrong vial number → |__|__|__|__|__| [N] ☐ Not administered → Please complete below (*)	Oral

(*) ***Why not administered?***

→ Please tick (✓) the major reason for non administration

☐ [SAE] Serious adverse event: → Please complete and submit **SAE** report
→ Please specify SAE No. |__|__|

☐ [OTH] Other, please specify: _____
(e.g.: consent withdrawal, Protocol violation, AE…)

→ Please tick who made the decision: → [I] ☐ Investigator [P] ☐ Parents/Guardians

IMMEDIATE POST-VACCINATION OBSERVATION

If any serious adverse events occurred during the immediate post-vaccination time (30 minutes) please fill in the **Serious Adverse Event** report**.**

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.

12.

AMENDMENT 5

VISIT 4

MONTH 3

30 – 48 days after Visit 3

AMENDMENT 5

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

HIV TESTING RESULTS

Please communicate the results of the HIV test to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed.
If HIV not yet performed, offer HIV pre test counselling and HIV informed consent.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

13.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__|.|__| kg

LABORATORY TESTS

BLOOD SAMPLE (2 ml for all subjects in South Africa and 1ml for all subjects in Malawi)

Has a blood sample been taken for Rota assay ?

☐ Yes → Please complete only if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

☐ No

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode between Visit 3 and Visit 4 ?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis section.

HIV TEST

(HIV testing should be proposed to all subjects who were not tested previously).
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.
☐ No

AMENDMENT 5

VISIT 5
21 – 48 days after Visit 4

Only in subjects with HIV test at visit 4.

HIV TESTING RESULTS

Please communicate HIV test result from test done at visit 4 to parents/guardians and post-test counselling.
Please perform a confirmatory HIV test if needed and plan a contact to inform the parents/guardians about the results.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**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.

☐ Visit 5 not applicable (subject did not perform a HIV test at visit 4)
☐ 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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

15.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 5**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

GASTROENTERITIS EPISODE

Did the subject present any gastroenteritis between visit 4 and visit 5 ?

☐ Yes → Please ensure a stool sample was collected.
→ Please fill in the gastroenteritis episode section.

☐ No

16.

AMENDMENT 5

VISIT 6

1 year of age

343 – 391 days of age

AMENDMENT 5

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 (leading to drop out) or a **Serious Adverse Event (SAE)** report, as appropriate. SAE reports must be faxed to GSK Biologicals Study Contact for SAE reporting within 24 hours from the time you become aware of the SAE.

GASTROENTERITIS

Please report any gastroenteritis and stool collection in the gastroenteritis section.
A stool sample must be collected for every gastroenteritis episode, within 7 days of the gastroenteritis start date.

MEDICATION / VACCINATION

Please report medication as specified in the Protocol and fill in the **Medication** section.

Please report concomitant vaccination in the **Concomitant Vaccination** section.

HIV TEST

Offer a HIV pre-test counselling and the HIV informed consent if a HIV test is proposed between visit 4 and visit 6.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit		Subject Number
102248		**VISIT 6**		|__|__|__|__|__|

CHECK FOR STUDY CONTINUATION

Did the subject return for visit 6 ?

☐ 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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event (leading to drop out)
→ 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

17.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol		Visit	Date of visit	Subject Number
102248		**VISIT 6**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present any gastroenteritis episode since last visit and Visit 6 ?

☐ No

☐ Yes → please ensure a stool sample was collected.
→ please fill in the gastroenteritis episode section.

HIV TEST

(HIV testing should be proposed if a child develops symptoms indicative of AIDS (WHO interim stage III or IV) or has to be hospitalized with SAE, and HIV testing has not yet been performed.)
Was a HIV test performed on the subject since last visit ?

☐ Yes → Please complete the specific HIV section.

☐ No

HIV REPEAT TEST

Was a blood sample taken after breast feeding cessation (repeat test for subjects HIV negative by PCR) ?

☐ Yes → |__|__| |__|__|__| |__|__|__|__| *(please fill in only if different from visit date)*
day month year

→ HIV testing result (PCR) :

☐ Negative
☐ Positive
☐ Unknown

☐ No

☐ NA

18.

AMENDMENT 5

GASTROENTERITIS EPISODES

VISIT 1 – VISIT 6

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|

Has any gastroenteritis occurred from Visit 1 until Visit 6 ?
☐ No
☐ Yes → Please complete below and next pages if necessary.

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__|.|__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

20.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

22.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

24.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No ☐ Yes → If yes: *(please tick one box only)* ☐ Oral rehydration therapy ☐ IV rehydration therapy ☐ Oral and IV rehydration therapy ☐ Other, please specify: _____

Dehydration: ☐ No ☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No ☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

26.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|__|__|__|__|__|__|

Episode N° |__|__|

Treatment: ☐ No
☐ Yes → If yes: *(please tick one box only)*
☐ Oral rehydration therapy
☐ IV rehydration therapy
☐ Oral and IV rehydration therapy
☐ Other, please specify: _____

Dehydration: ☐ No
☐ Yes → If yes: ☐ 1 – 5% ☐ ≥ 6%

Hospitalisation: ☐ No
☐ Yes

One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.
A second stool sample can be taken if the first one is insufficient.

Stool collection date and time: 1st stool : |__|__| |__|__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

2nd stool : |__|__| |__|__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Daily details of the GE episode :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|__|__| |__|__|__| |__|__|__|__|	|__|__|	|__|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 6		Subject Number
102248			|_|_|_|_|_|_|

Daily details of the GE episode (continued) :

Report every day of the GE. day month year	Number of looser than normal stools* per day	Number of vomiting per day	Temperature °C	[A] ☐ Axillary (recommended) [O] ☐ Oral [R] ☐ Rectal	Less playfull / Irritability	Lethargic	Listless	Seizure
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown
|_|_||_|_|_||_|_|_|_|	|_|_|	|_|_|	|_|_|.|_|	☐ not taken	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown	☐ No ☐ Yes ☐ Unknown

*The first and last date of the gastroenteritis episode must have at least 3 looser than normal stool.

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AMENDMENT 5

HIV SECTION

REMINDERS

- HIV pre-test counselling and HIV ICF must be offered before any HIV procedure.
- HIV post-test counselling must be offered to all subjects who agreed to a HIV testing.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

Did the subject have any HIV test performed during the study period ?

☐ Yes → please continue filling the sections here below.
☐ No → please ignore the following questions.

INITIAL HIV TEST

Was a HIV informed consent signed ?

☐ Yes → please indicate the date at which the ICF was signed : |__|__| |__|__|__| |__|__|__|__|
day month year

→ please continue filling the sections here below.

☐ No (please do not record any HIV results in the CRF)

Was a blood sample taken for the initial HIV testing ?

☐ Yes → please specify the date at blood sample collection : |__|__| |__|__|__| |__|__|__|__|
day month year

→ please record result here below :

HIV Elisa/Rapid test

☐ Negative
☐ Positive
☐ Unknown
☐ Not done
☐ NA → only for subjects whose mothers are known to be HIV +

PCR test

☐ Negative
☐ Positive
☐ Unknown
☐ Not done
☐ NA → if Elisa/Rapid test negative

☐ No

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

INITIAL HIV TEST (continued)

Was the initial HIV test result communicated to the parent ?

☐ Yes → please specify the date at which the result was communicated |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No → please specify reason :
- ☐ Subject lost to follow-up
- ☐ Subjects parents/guardians refuse to receive test result
- ☐ Others : _____

Is a confirmatory HIV test required ?

Yes → please continue filling the information here below.
No → please ignore the following question.

CONFIRMATORY HIV TEST

Was a blood sample taken for the HIV confirmatory test :

☐ Yes → please specify date of blood sample collection : |__|__| |__|__|__| |__|__|__|__|
day month year

→ please record result here below :
- ☐ Negative
- ☐ Positive
- ☐ Unknown

☐ No → please specify reason :
- ☐ Subject lost to follow-up
- ☐ Subjects parents/guardians refuse confirmatory test
- ☐ Others : _____

Was the HIV confirmatory test result communicated to the parent ?

☐ Yes → please specify the date at which the result was communicated |__|__| |__|__|__| |__|__|__|__|
day month year

☐ No → please specify reason :
- ☐ Subject lost to follow-up
- ☐ Subjects parents/guardians refuse to receive test result
- ☐ Others : _____

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AMENDMENT 5

CONCOMITANT VACCINATION

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

- All vaccines administered in the period beginning at birth and ending at study end should be documented in the CRF with trade name, route of administration and date(s) of administration.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered since birth (except OPV and DTPw-HB/Hib given at visit 1,2 and 3)?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, route and vaccine administration date.

Trade / (Generic) Name	Route	Administration date day month year
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		
		|__|__||__|__|__||__|__|__|__|
For GSK		

ID	= Intradermal	PE	= Parenteral
IH	= Inhalation	PO	= Oral
IM	= Intramuscular	SC	= Subcutaneous
IV	= Intravenous	SL	= Sublingual
NA	= Intranasal	TD	= Transdermal
OTH	= Other	UNK	= Unknown

31.

AMENDMENT 5

MEDICATION

AMENDMENT 5

GlaxoSmithKline Biologicals

- Medication route. Please use below defined codes.

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

At each study visit/contact, the investigator should question the subject/subject's parents/guardians 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 at Visit 1 and ending at 31 days post last vaccine dose are to be recorded with generic name of the medication (trade names are allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.
- Any treatments and/or medications specifically contraindicated, e.g., any immunoglobulins, other blood products and any immune modifying drugs administered since birth until one month (minimum 30 days) after the last dose of the study vaccine or placebo are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.
- A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever [rectal temperature < 38°C, oral temperature < 37.5°C or axillary temperature < 37.5°C] and any other symptom, to prevent fever from occurring). Any concomitant medication administered prophylactically in anticipation of reaction to the vaccination must be recorded in the CRF 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 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 administered throughout the study (from Visit 1 to Visit 6) must be recorded in the CRF.
- Any ARV therapy given throughout the study (from Visit 1 to Visit 6) must be recorded in the CRF.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	Book			Subject Number
102248				|_|_|_|_|_|_|

MEDICATION

Have any medications/treatments been administered during the timeframe as specified in the Protocol ?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or tick box if continuing at end of study (day month year)	
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					
	☐ Prophylactic			Start: |_|_| |_|_|_| |_|_|_|_| End: |_|_| |_|_|_| |_|_|_|_|	☐
For GSK					

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol	Book			Subject Number
102248				|__|__|__|__|__|__|

MEDICATION (continued)

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					

33.

AMENDMENT 5

NON-SERIOUS ADVERSE EVENTS

TO BE FILLED ONLY IN CASE OF DROP-OUT DUE TO NON-SERIOUS AE

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP- OUT

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** report).

Has any **non-serious adverse event (leading to drop-outs)** occurred since Visit 1 until Visit 6 ?

☐ 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

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS LEADING TO DROP OUT (continued)

AE No.	**3**	**4**
Description	_____ _____ _____	_____ _____ _____
For GSK		
Date Started	|__|__|__|__|__|__|__|__| day month year ☐ during immediate post-vaccination period (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

AMENDMENT 5

STUDY CONCLUSION

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|_|_|_|_|_|_|

STUDY CONCLUSION

OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event during the study period ?

☐ No ☐ Yes → Specify total number of SAE's: |_|_|

STATUS OF TREATMENT BLIND

Was the treatment blind broken during the study?

☐ 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 the **Serious Adverse Event** report as appropriate.

ELIMINATION CRITERIA

Did any elimination criteria become applicable during the study?

☐ No ☐ Yes → Specify: _____

36.

AMENDMENT 5

GlaxoSmithKline

102248 (Rota-037)

Protocol				Subject Number
102248				|__|__|__|__|__|__|

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 report
→ Please specify SAE No. |__|__|

☐ [AEX] Non-Serious adverse event
→ Please complete Non-serious Adverse Event section
→ Please specify AE No. |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event.

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [OTH] Other, please specify: _____

→ Who made the decision: [I] ☐ Investigator [P] ☐ Parents/Guardians

→ Date of last contact: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Was the subject in good condition at date of last contact?

☐ No → Please specify: _____

☐ 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: _____

37.

GlaxoSmithKline

Protocol	DIARY CARD		Subject number
102248 (Rota-037)		**DOSE 1**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Please fill in below and assess the occurrence of any gastroenteritis according to the criteria listed hereafter.

Temperature:
Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS: is defined as presence of diarrhea with or without vomiting.

DIARRHEA: defined as passage of three or more looser than normal stools or watery stools within 24 hours.

VOMITING: defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours.

- **Please collect stools samples in case of diarrhea, record whether medical treatment has been taken.**
- **One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.**
- **A second stool sample can be taken if the first one is insufficient.**

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____
Temperature, °C ☐ Axillary **(recommended)** ☐ Oral ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
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

GlaxoSmithKline

Protocol	DIARY CARD		Subject number
102248 (Rota-037)		**DOSE 1** Visit 1 – Visit 2	|_____|

MEDICATION

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify: _____

Please fill in below and record any medication taken:

MEDICATION	**Please fill in below if any medication has been taken since the vaccination (excluding medication taken in case of gastroenteritis episode)**				
Trade/Generic name	**Reason**	**Total Daily Dose**	**Start date** day month year	**End date or check box if continuing** day month year	
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐
			|__|___|____|	|__|___|____|	☐

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |_____| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

GlaxoSmithKline

Protocol	DIARY CARD		Subject number
102248 (Rota-037)		**DOSE 2**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Please fill in below and assess the occurrence of any gastroenteritis according to the criteria listed hereafter.

Temperature:
Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS: is defined as presence of diarrhea with or without vomiting.

DIARRHEA: defined as passage of three or more looser than normal stools or watery stools within 24 hours.

VOMITING: defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours.

- **Please collect stools samples in case of diarrhea, record whether medical treatment has been taken.**
- **One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.**
- **A second stool sample can be taken if the first one is insufficient.**

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____
Temperature, °C ☐ Axillary **(recommended)** ☐ Oral ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
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

GlaxoSmithKline

Protocol	DIARY CARD		Subject number
102248 (Rota-037)		**DOSE 2** Visit 2 – Visit 3	|__|__|__|__|__|__|

MEDICATION

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify: _____

Please fill in below and record any medication taken:

MEDICATION	**Please fill in below if any medication has been taken since the vaccination (excluding medication taken in case of gastroenteritis episode)**				
Trade/Generic name	**Reason**	**Total Daily Dose**	**Start date** (day month year)	**End date or check box if continuing** (day month year)	
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|__|__|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

GlaxoSmithKline

Protocol	DIARY CARD		Subject number
102248 (Rota-037)		**DOSE 3**	|__|__|__|__|__|__|

GASTROENTERITIS EPISODES

Please fill in below and assess the occurrence of any gastroenteritis according to the criteria listed hereafter.

Temperature:
Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS: is defined as presence of diarrhea with or without vomiting.

DIARRHEA: defined as passage of three or more looser than normal stools or watery stools within 24 hours.

VOMITING: defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within 24 hours.

- **Please collect stools samples in case of diarrhea, record whether medical treatment has been taken.**
- **One single stool sample should be collected as soon as possible and not later than 7 days after the beginning (preferably) of the gastroenteritis.**
- **A second stool sample can be taken if the first one is insufficient.**

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____	**Date** ____
Temperature, °C ☐ Axillary **(recommended)** ☐ Oral ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Irritability / Less playful?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Lethargic?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Listless?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Seizure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
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

GlaxoSmithKline

Protocol	DIARY CARD		Subject number
102248 (Rota-037)		**DOSE 3** Visit 3 – Visit 4	|__|__|__|__|__|__|

MEDICATION

MEDICATION FOR DIARRHEA:

- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ No medication
- ☐ Other, please specify: _____

Please fill in below and record any medication taken:

MEDICATION	**Please fill in below if any medication has been taken since the vaccination (excluding medication taken in case of gastroenteritis episode)**				
Trade/Generic name	**Reason**	**Total Daily Dose**	**Start date** day month year	**End date or check box if continuing** day month year	
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐
			|__||__|__|__||__|__|__|__|	|__||__|__|__||__|__|__|__|	☐

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|__|__|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

102248/ETR (Rota-037)

Gastroenteritis

Visit 1 – Visit 2 (dose 1)

Subject number: _____

Subject initials: _____

Dose _____

Vaccination Date |_|_| **Day** |_|_|_| **Month** |_|_|_|_| **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from day 0 of visit 1 (dose1) until visit 2 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 1 – Visit 2 (dose 1)

Subject number: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from day 0 of visit 1 (dose1) until visit 2 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 2 – Visit 3 (dose 2)

Subject number: _____

Subject initials: _____

Dose _____

Vaccination Date |_|_| **Day** |_|_|_| **Month** |_|_|_|_| **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from day 0 of visit 2 (dose 2) until visit 3 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 2 – Visit 3 (dose 2)

Subject number: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from visit 2 (dose 2) until visit 3 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 3 – Visit 4 (dose 3)

Subject number: _____

Subject initials: _____

Dose _____

Vaccination Date |_|_| **Day** |_|_|_| **Month** |_|_|_|_| **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from day 0 of visit 3 (dose 3) until visit 4 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ Oral rehydration
→ IV rehydration
→ Oral /IV rehydration
→ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ Oral rehydration
→ IV rehydration
→ Oral /IV rehydration
→ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 3 – Visit 4 (dose 3)

Subject number: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from visit 3 (dose 3) until visit 4 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 4 – Visit 6

Subject number: _____

Subject initials: _____

Dose _____

Vaccination Date |_|_| **Day** |_|_|_| **Month** |_|_|_|_| **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from visit 4 until visit 6 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date:	0 4	D E C	2 0 0 5
	Day	Month	Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given for the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____

No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given for the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____

No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ Oral rehydration
→ IV rehydration
→ Oral /IV rehydration
→ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ Oral rehydration
→ IV rehydration
→ Oral /IV rehydration
→ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Gastroenteritis

Visit 4 – Visit 6

Subject number: _____

Dose _____

Visit Date |_|_| **Day** |_|_|_| **Month** |_|_|_|_| **Year**

Please remember to bring back the diary card on ____/_____/____

In case of hospitalisation or serious adverse event, please inform _____

- Please assess the occurrence of any gastroenteritis from visit 4 until visit 6 and detail the symptoms daily until the end of the gastroenteritis

- A **gastroenteritis** is defined as presence of diarrhoea with or without vomiting

- A **diarrhoea** is defined as passage of three or more looser than normal stools or watery stools within 24 hours (1 day).

- **Vomiting** is defined as one or more episodes of forceful emptying of partially digested stomach contents more than (≥) 1 hour after feeding within 24 hours.

- **Temperature**: Please record the infants temperature every day. If the infants temperature has been taken more than once a day, please report highest value for the day.

- A stool sample should always be collected in the event of diarrhoea. This stool sample should collected within 7 days after GE onset date.

- Any medication given for diarrhoea should be reported

- Please complete the date as follows: Eg. 4December 2005

Date: | **0** | **4** | **D** | **E** | **C** | **2** | **0** | **0** | **5** |
Day Month Year

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature

Axillary ☐☐.☐ °C

Rectally ☐☐.☐ °C

Vomiting

Number of vomits ☐

Stools

Total number of stools ☐

Aspect: number of normal stools ☐

number of looser than normal stools ☐

Stool sample taken: Yes ☐

No ☐

Was any medication given for the diarrhoea?: Yes ☐

→ ☐ Oral rehydration

→ ☐ IV rehydration

→ ☐ Oral /IV rehydration

→ ☐ Other, please specify _____

No ☐

Hospitalisation for diarrhoea: Yes ☐

No ☐

Irritability / Less playful: Yes ☐

No ☐

Lethargic: Yes ☐

No ☐

Listless: Yes ☐

No ☐

Seizure: Yes ☐

No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given for the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐.☐ °C
Rectally ☐☐.☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools
Aspect: number of normal stools
number of looser than normal stools
Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No
Irritability / Less playful: Yes
No
Lethargic: Yes
No
Listless: Yes
No
Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary ___ . ___ °C
Rectally ___ . ___ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: Day Month Year

Temperature
Axillary . °C
Rectally . °C

Vomiting
Number of vomits

Stools
Total number of stools

Aspect: number of normal stools
number of looser than normal stools

Stool sample taken: Yes
No

Was any medication given
For the diarrhoea?: Yes
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No

Hospitalisation for diarrhoea: Yes
No

Irritability / Less playful: Yes
No

Lethargic: Yes
No

Listless: Yes
No

Seizure: Yes
No

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

Date: ☐☐ Day ☐☐☐ Month ☐☐☐☐ Year

Temperature
Axillary ☐☐ . ☐ °C

Vomiting
Number of vomits ☐

Stools
Total number of stools ☐
Aspect: number of normal stools ☐
number of looser than normal stools ☐
Stool sample taken: Yes ☐
No ☐

Was any medication given
For the diarrhoea?: Yes ☐
→ ☐ Oral rehydration
→ ☐ IV rehydration
→ ☐ Oral /IV rehydration
→ ☐ Other, please specify
_____
No ☐

Hospitalisation for diarrhoea: Yes ☐
No ☐
Irritability / Less playful: Yes ☐
No ☐
Lethargic: Yes ☐
No ☐
Listless: Yes ☐
No ☐
Seizure: Yes ☐
No ☐

102248/ETR (Rota-037)

Medications

Visit 1 – Visit 2 (dose 1)

Subject number: _____

Subject Initials: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

- Please record any medication taken from visit 1 till visit 2

(excluding for GE)

- Please complete the date as follows: Eg. 4December 2005

Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

102248/ETR (Rota-037)

Medications

Visit 1 – Visit 2 (dose 1)

Subject number: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

- Please record any medication taken from visit 1 till visit 2

(excluding for GE)

- Please complete the date as follows: Eg. 4December 2005

Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

102248/ETR (Rota-037)

Medications

Visit 2 – Visit 3 (dose 2)

Subject number: _____

Subject Initials: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

- Please record any medication taken from visit 2 till visit 3

(excluding for GE)

- Please complete the date as follows: Eg. 4December 2005

Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

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Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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Reason: _____

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Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

102248/ETR (Rota-037)

Medications

Visit 2 – Visit 3 (dose 2)

Subject number: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

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Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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day month year

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Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

102248/ETR (Rota-037)

Medications

Visit 3 – Visit 4 (dose 3)

Subject number: _____

Subject Initials: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

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Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

102248/ETR (Rota-037)

Medications

Visit 3 – Visit 4 (dose 3)

Subject number: _____

Dose _____

Vaccination Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

- Please record any medication taken from visit 3 till visit 4

(excluding for GE)

- Please complete the date as follows: Eg. 4December 2005

Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

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Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

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Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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day month year

Medication

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Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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day month year

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Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

102248/ETR (Rota-037)

Medications

Visit 4 – Visit 6

Subject number: _____

Subject Initials: _____

Dose _____

Vaccination Date |_|_| **Day** |_|_|_| **Month** |_|_|_|_| **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

- Please record any medication taken from visit 4 till visit 5

(excluding for GE)

- Please complete the date as follows: Eg. 4December 2005

Date: | 0 | 4 | | D | E | C | | 2 | 0 | 0 | 5 |
Day Month Year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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Start Date: __ __ / __ __ __ / __ __ __ __
day month year

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Name: _____

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Start Date: __ __ / __ __ __ / __ __ __ __
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Start Date: __ __ / __ __ __ / __ __ __ __
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Medication

Name: _____

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Start Date: __ __ / __ __ __ / __ __ __ __
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day month year

102248/ETR (Rota-037)

Medications

Visit 4 – Visit 6

Subject number: _____

Dose _____

Visit Date |_|_| |_|_|_| |_|_|_|_|
Day **Month** **Year**

Please remember to bring back the diary card on _____/_____/_____

In case of hospitalisation or serious adverse event, please inform _____

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Day Month Year

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Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
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day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ / __ __ __ / __ __ __ __ or ongoing? ____
day month year

Medication

Name: _____

Reason: _____

Daily Dose: _____

Start Date: __ __ / __ __ __ / __ __ __ __
day month year

End Date: __ __ /__ __ __ / __ __ __ __ or ongoing? ____
day month year

List of Independent Ethics Committees /Institutional Review Boards

Independent Ethics Committees /Institutional Review Boards

Centre Number(s) *	Ethics Review Body	Location
[redacted]	[redacted]	Malawi

Centre Number(s) *	Ethics Review Body	Location
[redacted]	[redacted]	
[redacted]	[redacted]	**South Africa**

Centre Number(s) *	Ethics Review Body	Location
[redacted]	[redacted]	

* GSK Biologicals assigned centre number

Representative written information for patient and sample consent forms

WRITTEN INFORMED CONSENT FORM FOR SUBJECTS ENROLLED IN MALAWI

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Simplified Study Title: A study to find out if the vaccine protects against diarrhoea and if 2 doses of the HRV vaccine are as good as 3 doses in their ability to protect against diarrhoea caused by rotavirus, and to determine if they are safe when this vaccine is given with routine childhood vaccinations in healthy infants.

Version Number: 10 Malawi-specific version **Date:** 03/08/2006

Company Name: GlaxoSmithKline Biologicals

Subject Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Purpose/Description/Procedures/Duration

Rotavirus is a leading cause of severe diarrhoea among children. GSK Biologicals, a drug company that tests new vaccines and drugs has developed a new vaccine- the human rotavirus vaccine (referred to as HRV vaccine), for protection of children from developing this type of diarrhoea. The purpose of this research is to find out if the vaccine protects against diarrhoea and if 2 doses of this new vaccine are as good as 3 doses, both in terms of providing protection and in being safe. The vaccine that is being tested has to be taken by mouth, (like the polio drops). We wish to invite your child to take part in this research study.

GSK Biologicals' HRV vaccine (Rotarix™) is registered in Malawi and may become available in the private market at a later stage.

The main objective of this document, called a consent form, is to provide you as the parents or guardians of a child with information necessary to help you make the decision about whether or not to have your child in this study. The document provides information about the vaccine including the likely advantages and disadvantages associated with the vaccine, the study purpose and the study procedures. This document also tells you about your rights and responsibilities on behalf of your child if you decide to enrol him/her in the study as a participant

This consent form may contain words that you do not understand. Please ask the study doctor or staff to explain anything unfamiliar, and to answer any questions that you have about the study.

In order to help you in understanding this study; you will receive a 3-page summary of this consent form.

You will be asked to complete an Informed Consent Feedback Form. Your answers to the questions in this form will allow the person taking informed consent to understand if there are any points that you did not understand. In that case, the informed consent will be again explained to you.

Once you understand the study, you will be asked if you want your child to be in the study. If you do, you will be asked to sign this form.

The study doctor and/or the institution are paid to conduct this research study by two international organisations: the World Health Organisation (WHO) and the Rotavirus Vaccine Program LLC (RVP). GlaxoSmithKline Biologicals (GSK) is responsible for administration of the study including clinical trial supply management, clinical data collection, analysis and biological samples analysis.

This medical research study will be conducted on 5670 infants coming for their routine immunisation visits to the study centers in Malawi and South Africa. All healthy infants between the ages of 5-10 weeks can take part in this study.

All children participating in this study will have five study visits (Visits 1, 2, 3, 4 and 6). The study staff will inform you if your child may have one additional visit (Visit 5) and/or contact depending on if and when the HIV test is done and whether a confirmatory HIV test is done. During the study, a member of the study staff will visit you at home weekly.

The main purpose of this study is to find out how well the HRV vaccine works to prevent severe cases of rotavirus diarrhoea. This will be done by giving some children the HRV vaccine and some children a placebo (product that looks like the real vaccine, but does not contain any active ingredient), and comparing the results. We will take stool samples from each child with diarrhoea for testing to find the number of rotavirus diarrhoea cases. This will allow us to assess the effectiveness of the HRV vaccine (ability to prevent rotavirus diarrhoea). We will also look for any serious side effects to evaluate safety of HRV vaccine. We will take a blood sample (± 1 ml which is a bit less than a quarter teaspoon) from some children at the first visit for baseline values. A blood sample (± 1

ml which is a bit less than a quarter teaspoon) will be taken from all children at Visit 4 to see how your child's immune system (part of body that fights infection) reacts to the vaccines.

Since HIV infected children may respond differently to the vaccine, it would be ideal to test recruited infants for HIV. Thus, testing for HIV will be offered for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4. You will be asked to sign a separate consent form to allow HIV testing. You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling and then a blood sample (± 1 ml which is a bit less than a quarter teaspoon) will be taken from your child to perform the HIV test. You will be informed of the test results at the following visit and post-test counselling will be offered. If necessary, a blood sample (± 1 ml which is a bit less than a quarter teaspoon) will be taken from your child for a confirmatory HIV test. Depending on when the HIV test is done and whether a confirmatory HIV test is done, your child may have one additional visit (Visit 5) and/or contact so that the study staff can inform you of the HIV test results and offer further counselling. The study staff will inform you if your child will require additional visit and/or contact.

If your child is tested and found to be HIV exposed and/or HIV positive, the study staff will provide cotrimoxazole prophylaxis for the duration of study follow-up. At study end, your child will be referred to the cotrimoxazole service provided by the Ministry of Health. If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.

Ethical and Regulatory Approval

This clinical study protocol has been submitted to: 1) [redacted] 2) [redacted] 3) [redacted] 4) [redacted] These committees have granted written approval.

The study has been structured in accordance with the 2004 version of Declaration of Helsinki, which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained should you wish to review it.

Study Participation

The duration of this study is for a maximum period of 10 to 11 months. All children participating in this study may have five study visits (Visits 1, 2, 3, 4 and 6). The study staff will inform you if your child may have one additional visit (Visit 5) and/or contact depending on when the HIV test is done and whether a confirmatory HIV test is done.

During the study, a member of the study staff will visit you weekly to assist/advise you with any problems you may have.

If you are interested to take part in the research, the research staff will ask you questions about your child's medical history and the medicines that your child may be taking. Your child will not be able to participate in the study if she or he is taking certain kinds of medicines or has certain specific illnesses.

In this study one third of the children will get 3 doses of vaccine, another third will get 2 doses of vaccine and one dose of placebo (an inactive product that looks like the vaccine but has no effect on the body), and the remaining third will get 3 doses of placebo. Randomisation will be used to assign children to one of the three treatment groups. Randomisation means that the participants are put into a group by chance. It is like flipping a coin. Your child will have a 2 out of 3 chance of receiving the HRV vaccine (either three doses of HRV vaccine or two doses of HRV vaccine and one dose of placebo) and a 1 out of 3 chance of receiving a placebo (looks like vaccine but has no activity). Neither you nor your doctor will know whether your child receives the real vaccine or the inactive liquid. If needed in case of emergencies, however, the doctor will be given this information. We need to give inactive placebo to some children to make sure that the effect we see after our research has not occurred because of chance, but occurred because of the vaccine. This is the way that scientific studies are designed.

If your child is eligible to take part in the trial, he/she will receive three doses given four weeks apart. The study vaccine or placebo will be given by mouth. All study participants will be observed closely for at least 30 minutes following the administration of vaccines to monitor any reaction to the vaccine/placebo. As mentioned before, neither the doctor nor you will know what your child has received, but your child will be followed up very carefully to make sure that he gets medical attention when required.

Your child will receive his/her nationally recommended routine vaccinations at the same time of the administration of the study vaccine dose. This study in no way alters the routine immunisation schedule, and it is very important for you to follow the recommendations given by the immunisation nurse or Health Surveillance Assistant.

The study is expected to end when your baby will be one year old. The study procedures are summarised below. The study nurse will review all the study procedures with you in detail.

- At Visits 1, 2 and 3 that will take place four weeks apart, the doctor will examine each child and give a dose of HRV or its placebo by mouth. At each of these visits, you will receive two diary cards to collect information on diarrhoea and information on any medicines that your child has received. The study staff will train you on how to complete these diary cards.
- Each child will also receive all the routine vaccines at Visits 1, 2 and 3. For other routine vaccinations (at 9 months of age), you will be requested to take your child to your local clinic.
- Visits 4, 5 and 6 are follow-up visits.

- Visit 4 will take place one month after Visit 3.
- Visit 5 may only take place if your child had an HIV test at Visit 4. The HIV test results will be communicated to you at this visit and blood sample for confirmatory HIV test will be taken if necessary. The study staff will inform you if a contact is needed so that results of the confirmatory HIV test can be communicated to you. There will no other study procedures.
- Visit 6 will be the final visit and will take place when your child is one year old.

- Visit 1 will take about 1 ½ to 2 hours and the following study visits (2, 3, 4, 5 and 6) should take around 1 hour to complete.
- At each visit, the investigator will ask you if your child has been sick or hospitalised since the previous visit.
- A blood sample (± 1 ml which is a bit less than a quarter teaspoon) will be collected from the most convenient and safe site, most probably from an arm vein, from one in ten infants in Malawi at Visit 1. Your child may be one of these infants from whom blood is taken at visit 1. This blood sample will be tested to measure the baseline amount of substance in the blood that fights infection (called antibodies).
- A blood sample (± 1 ml which is a bit less than a quarter teaspoon) will be collected from the most convenient and safe site, most probably from an arm vein, from all infants, including your child, at Visit 4. This blood sample will be tested to measure the amount of substance in the blood that fights infection (called antibodies). This will allow the researchers to see how your child reacts to the vaccines to fight infection (called immune response).
- In order to best evaluate the response to the vaccine, HIV (human immunodeficiency virus) testing of all infants should be ideally performed during the study. Testing for HIV will be offered and ideally performed at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4. At Visit 1, the study staff will ask whether your child has been exposed to HIV. A separate Informed Consent form will be provided to you at Visit 1 to seek your permission to perform HIV testing for your child. You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling and then a blood sample (± 1 ml which is a bit less than a quarter teaspoon) will be taken from your child to perform the HIV test. At Visit 1, this will be done by a heel prick, unless your child is part of the one in ten infants already having blood taken from an arm vein. At Visit 4 your child will not require an additional needle prick for HIV testing as blood will already be taken from an arm vein at this visit. You will be informed of the test results at the following visit and post-test counselling will be offered. If necessary, a blood sample (± 1 ml which is a bit less than a quarter teaspoon) will be taken from your child at the following visit for a confirmatory HIV test. This will be done by a heel prick. Depending on when the HIV test is done and whether a confirmatory HIV test is done, your child may

have an additional visit (Visit 5 approximately 3-6 weeks after Visit 4) and/or contact.

- If your child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised and any HIV testing has not yet been performed, HIV testing, counselling and the concerned Informed Consent will be proposed to you in the hospital. If HIV testing is performed in the hospital, the test will not be repeated at Visit 4. A confirmatory HIV test will be performed as necessary.
- If your child is tested and found to be HIV exposed and/or HIV positive, the study staff will provide cotrimoxazole prophylaxis for the duration of study follow-up. At study end, your child will be referred to the cotrimoxazole service provided by the Ministry of Health. If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.
- At the first visit, you will receive a Trial Identification Card, which will specify details of the trial, 24-hour telephone number of the study doctor, study nurses and study staff.
- During the study, a member of the study staff will visit you weekly to check if your child had any diarrhoea. Each home visit will take about half an hour.
- If you feel that your child has symptoms of severe diarrhoea, you should take him/her to the nearest hospital/medical facility. The hospital/medical facility that is currently nearest to you is: _____. You should show the Trial Identification Card to any health care professional that you consult.
- You should contact your health care practitioner at your health center immediately should your child manifest any signs or symptoms that you perceive as serious. The study staff will be available to your health care practitioner from the nearest health center for consultation for the entire study period (24 hours/day).
- When your child has diarrhoea, you will be asked to complete a Diary Card daily until end of diarrhoea. The information requested on the Diary Cards includes taking your child's temperature and noting information on the diarrhoea episode. The study staff member will help you to complete the diary card during the weekly visits.
- You will be asked to take stool samples from your child if he/she develops diarrhoea at any time from Visit 1 to Visit 6. Containers for collection of stool samples will be provided to you. You will be asked to either contact your Health Surveillance Assistant to pick up the sample or bring the sample to the centre, within 24 hours of collection.
- A part of the collected stool sample will be stored as back-up of specimens in case of loss during shipment.

- If you agree, collected samples may be stored for up to 15 years for further testing for the disease under study (no genetic testing).
- Collected samples may undergo additional testing to further evaluate the immunogenicity of the vaccine as needed.

Your responsibilities are:

- to follow the instructions given by the study doctor and the study staff,
- to stay in the same area for the coming year,
- to bring your child to the clinic at scheduled visits and to answer the final questions at the end of the study,
- to take a stool sample from your child if he/she has diarrhoea and either contact your Health Surveillance Assistant to pick up the sample or bring the sample to the centre, within 24 hours of collection,
- to complete the information requested on the Diary Cards which includes taking your child's temperature and noting information on the diarrhoea episode and information on any medicine that your child has received,
- to promptly report to the study staff should your child develop an illness that you perceive as serious or undergo hospitalisation.

If you want to stop your child's participation in the study or if you find you have not followed instructions listed above, it is important that you notify the study doctor or study staff.

Number of Subjects

This study will involve a total of approximately 5670 infants at several sites in Malawi and South Africa. A minimum of 2670 infants and up to 3070 infants are planned to be enrolled in Malawi.

Recruitment of new participants in this study will stop when the planned number of participants has been achieved.

The names of people who can be contacted for information on the trial and/or medical care

The physician you can contact if you require any additional information or have any questions concerning the trial, availability of medical care or if you think you have experienced a research-related illness or injury.

You may ask questions about the study. If you have any questions, please contact:

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Fax number of investigator:

Risks/Inconveniences

Over 80,000 adults, children, and infants have participated in studies with the rotavirus vaccine. During these studies, over 37,000 infants received at least one dose of the vaccine.

The rotavirus vaccine caused only mild side effects in some infants that were similar to those observed in infants who were given a placebo (product that looks like the real vaccine, but does not contain any active ingredient). The occurrence of irritability (fussiness) and loss of appetite were reported in more than 1 in 10 subjects. The following reactions were commonly (less than 1 in 10 subjects) reported: fever, fatigue, diarrhea, vomiting, flatulence (excessive gas), abdominal pain and regurgitation of food (bring back already swallowed food). The following were uncommonly (less than 1 in 100 subjects) or some even rarely reported (less than 1 in 1000): crying, sleep disorder, somnolence (sleepiness) and constipation, upper respiratory tract infection, hoarseness, rhinorrhoea (runny nose), dermatitis (inflammation of the skin), rash and muscle cramp.

The vaccine will not cause diarrhoea.

Seven years ago, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage of the small intestine that requires immediate attention by a doctor. If intussusception is recognised early, treatment can be given for complete recovery. Because RotaShield™ may have increased the risk of intussusception, it is no longer available. If you are interested, your doctor can give you more information on intussusception.

The rotavirus vaccine used in this study was tested in a large study with 63,225 children and results showed that this rotavirus vaccine being tested in this study does not increase the risk of intussusception.

There may be momentary, mild discomfort and bruising of the skin on the arm 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 or haemoglobin that may be caused due to loss of blood).

Your child will receive routine vaccinations (DTPw-HBV/Hib and OPV) during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, or crying.

As with any experimental vaccine, unexpected serious adverse experiences, including allergic reactions to the vaccine, may occur. All the medical equipment to treat any serious reactions to the study vaccine will be available.

You should contact the study contact person at your health center immediately should your child show any reactions that you are worried about.

You will be informed of any new findings developed during the course of this research study.

Benefits

If the vaccine is efficacious in this population, infants who receive the vaccine may have the benefit of being protected against rotavirus diseases. Infants who receive a placebo will not have this benefit, however if this vaccine proves to be useful, your child's participation will benefit other children in the future.

If your child is tested and found to be HIV exposed and/or HIV positive, the study staff will provide cotrimoxazole prophylaxis for the duration of study follow-up. At study end, your child will be referred to the cotrimoxazole service provided by the Ministry of Health. If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study.

At Visit 1 you will be given a health passport for your child and 8 nappies to assist with the collection of stool samples and a bed net will be offered to you. At every study visit you will be provided with a bar of soap for washing your hands after the collection of stool samples. At Visits 1 and 4 you will receive a pen to complete the diary cards. Multi-vitamin syrup for your child will be provided at Visits 3, 4, 5 and 6.

Alternative Treatment/Measure of Prevention

GSK Biologicals' HRV vaccine (Rotarix™) is approved for use in Malawi and may become available in the private market at a later stage.

Disease caused by rotavirus is treated with oral rehydration solutions or if necessary, intravenous fluid replacement. This is to prevent dehydration and shock. There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Joining this study is voluntary. If you decide against joining, there will be no penalty and your child will receive the routine vaccinations, as normal, by the health care centre. You and your child will lose no benefits to which you are otherwise entitled.

Compensation for Study-Related Injury

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI).

Broadly speaking the ABPI guidelines recommend that the sponsor, GlaxoSmithKline without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for the study. GlaxoSmithKline will not compensate you for any procedure carried out which is not in accordance with the protocol for the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. A copy of the guidelines for compensation for a possible injury/disablement that occurs while taking part in this study can be obtained from your doctor.

Payment to Subjects

You will receive no payment for your child's participation in this study.

Expenses/Costs

To help with the time and travel expenses, you will be reimbursed MK_200__ for each scheduled study visit completed by your child. There will be no charge for study-related doctor visits, examinations, and laboratory tests. All study vaccines will be provided free of charge.

If your child is referred to a HIV staging facility and/or ARV treatment centres during the study, transport will be offered through the study project or you will be given MK_____ to cover public transport costs to and from the ARV treatment site.

Right to ask questions and/or withdraw from the study

If you want any information regarding your child's rights as a research participant, or complaints regarding this research study, you may contact anyone of these independent committees established to help protect the rights of research participants.

Name of the Chairperson of Ethics Committee:_____

Name of the Ethics Committee**:** [redacted]

Address of Ethics Committee: [redacted]

Tel: [redacted]

Fax: [redacted]

Termination of Subjects' Study Participation

Your child's participation in the study may be stopped for any of the following reasons:

- If you do not follow the study doctor's instructions,
- The study doctor decides it is in the best interest of your child's health and welfare to discontinue participation in the study,
- There are either not enough subjects interested in participating in the study or the study has reached the required number of subjects,
- GSK Biologicals has decided to stop the study at this site for other reasons not known at this time,
- GSK Biologicals stops enrolling new subjects into study for any reason, and your child is in the screening phase of the study and has not yet been assigned to one of the vaccine groups.

Voluntary Participation and Subjects Right to End Participation

Your child's participation in this study is voluntary. If you do decide for your child to take part, you will be given this information to keep and be asked to sign this consent form. You may refuse your child's participation in this study, or once in the study you may decide to discontinue participation at any time. You must inform your study doctor if you decide to do this. Your decision to not let your child take part in the study or to stop participating in the study will not affect your child's current or future medical care, or any benefits to which your child may otherwise be entitled.

Any information and results collected before your child's withdrawal from the study will be used by GlaxoSmithKline.

Confidentiality and Data Privacy

Maintaining confidentiality is important to GlaxoSmithKline Biologicals, WHO and RVP. Your child's personal information (for example, gender, age, the details of his/her medical conditions) and other information (the data collected by GlaxoSmithKline Biologicals as part of the study) will be identified by a number (i.e., coded). Your child's name will not appear in any publications or reports produced from this study.

GlaxoSmithKline Biologicals will keep the information and the results collected about your child in this study. Your child's name and address are not included in the information kept by GlaxoSmithKline Biologicals - only your study doctor will keep this information. GlaxoSmithKline Biologicals has told your study doctor to keep the information about your child in a secure place. GlaxoSmithKline Biologicals will comply with internal procedures to protect personal and other information even in countries where data privacy laws are less strict than in Europe/US.

By agreeing to take part in this research study you will be allowing certain persons to see the information about your child (both personal, including his/her name, and other information) held by the study doctor. Your child's information will be looked at to confirm that it is correct and that it is related to your child. This will be done by selected people working for GlaxoSmithKline Biologicals and organisations acting on behalf of

GlaxoSmithKline Biologicals [redacted] along with the government regulatory authorities. These persons are required to maintain the confidentiality of your information.

Your child's information will be processed electronically (i.e., by a computer) or manually and analysed to determine outcome of this study. GlaxoSmithKline Biologicals may use your child's information for other medical/health care purposes related to development of this vaccine. For this purpose only your child's coded information will be used.

Your child's information may be sent to regulatory authorities, to the IEC/IRB, to other doctors and/or organisations working with GlaxoSmithKline Biologicals. It may also be sent to other GlaxoSmithKline Biologicals sites in this country and in other countries where there may be different or lesser standards for looking after it. GlaxoSmithKline Biologicals will apply the same standard in the protection of your information to the extent permitted by law.

You have the right to ask the study doctor about the data being collected on your child for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your child's personal information and to have any needed corrections to it made.

Future Use of Leftover Blood and/or Stool Samples

If you agree, collected blood and/or stool samples may be stored for up to 15 years and used for purposes related to testing for the disease under study and the quality assurance of laboratory tests. This may include the set up of new test methods as well as making sure that new tests are comparable to previous methods and work reliably. No genetic testing will be performed.

Samples will not be labelled with information that directly identifies you but will be coded with your study subject number.

Notification of New Information

Sometimes during the course of a research project, new information becomes available about the vaccine that is being studied. If this happens, we will tell you about new information that may affect you and your child willingness to stay in this study.

Consent statement

The HUMAN ROTAVIRUS vaccine study 102248 (Rota-037) has been clearly explained to me and I have read and understood the information provided [Written Informed Consent Form, Version number 10 Malawi-specific version, dated 03/08/2006, 15 pages].

I, , the Parent/Legal Guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child (subject)

hereby freely give my consent for my child to take part in this vaccine study.

I 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.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child to take part in this study.

I agree to take part in this study and to my child's participation in this study. I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any study-related questions during the study, or if I want to withdraw my child from the study.

> I give permission that the samples from my child are stored for up to 15 years for the purpose of further testing for the disease and vaccine under study or for quality assurance of laboratory tests, excluding genetic research.
>
> I do not give permission that the samples from my child are stored for up to 15 years.

Consent statement

***Signature (or thumb-print) of Parent/Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

***Printed name of Parent/Legal Guardian** _____

If the parent/legal guardian is illiterate, an Independent Literate Witness should also sign the consent form.

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

Informed Consent Feedback Form – Malawi Study Identification 102248 (Rota-037)
Subject's parent or legal guardian name _____
Subject number ____ ____ ____ ____ ____ Subject Initials ___ ___ ___

INFORMED CONSENT FEEDBACK FORM

This Informed Consent Feedback form will allow the person taking your consent to understand if there are any points of the Informed Consent you did not understand. In that case, the IC will be explained to you again.

Please may we ask you to take a few minutes of your time to complete this Informed Consent Feedback form? We would like you to choose the answer which you think is the MOST correct answer for each of the questions.

1) ***What does the rotavirus vaccine protect against?***

- ☐ **HIV/AIDS**
- ☐ **Diarrhoea caused by rotavirus**

2) ***Will your child receive the RV vaccine or a placebo?***

- ☐ **RV vaccine**
- ☐ **Placebo**
- ☐ **Either RV vaccine or Placebo**

3) ***How many visits (not counting this visit) will your child have to return for during the study at the most*****?**

- ☐ **2**
- ☐ **3**
- ☐ **5**

4) ***For how long will your child be followed up during the study?***

- ☐ **3 months**
- ☐ **6 months**
- ☐ **until 1 year old**

5) ***In case your child has an episode of diarrhoea, you should collect a stool sample and complete a diary card?***

- ☐ **True**
- ☐ **False**

Informed Consent Feedback Form – Malawi Study Identification 102248 (Rota-037)
Subject's parent or legal guardian name _____
Subject number ____ ____ ____ ____ ____ Subject Initials ___ ___ ___

6) ***Blood samples will be collected from your child?***

☐ **True**
☐ **False**

7) ***If you agree to participate in the study now, you can refuse HIV testing for your child at any time?***

☐ **True**
☐ **False**

8) ***If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study?***

☐ **True**
☐ **False**

9) ***In addition to the test products, you will get the routine EPI vaccinations at the Health Centre***

☐ **True**
☐ **False**

10) ***How often will the Health Surveillance Assistant (HSA) come to visit your child during the study?***

☐ **Once, every week**
☐ **Once, every month**

11) ***Do you have to carry the trial identification card with you at all times. Do you have to show it when you go to the clinic, to your doctor or hospital?***

☐ **Yes**
☐ **No**

12) ***In case of severe diarrhoea or any serious illness, you should go to the nearest hospital, show your trial identification card and inform study staff?***

☐ **True**
☐ **False**

13) ***Do you have to pay for the doctor's visit at the trial site and sample testing?***

☐ **Yes**

☐ **No**

14) ***This is a voluntary study; you will not receive any money for your child's participation in the study, but will receive a fixed amount of money to help with time and travel expenses for planned study visits.***

☐ **True**

☐ **False**

15) ***Once in the study, you have the right to ask questions at any time?***

☐ **True**

☐ **False**

16) ***Do you have the right to stop your child's participation in the study?***

☐ **Yes**

☐ **No**

17) ***Your child's personal information (name or other identifying particulars) will be made publicly available?***

☐ **True**

☐ **False**

Thank you for taking the time to complete this questionnaire.

Summary Informed Consent Form
Study Identification 102248 (rota-037)

CONFIDENTIAL

Study Rota-037- Information Sheet

1. What is the study about?

This study is about a vaccine against diarrhoeal disease due to rotavirus. In this study, children will be given two or three oral doses of the vaccine or three oral doses of placebo at the same time as the other vaccines given at your EPI centre. The placebo is a product that looks like the real vaccine, but does not contain any active ingredient. The placebo is used in studies where the effect of the vaccine has to be evaluated.

The objective of the study is to evaluate if the vaccine will prevent your child from getting rotavirus diarrhoea.

2. What is the vaccine for?

This is a new vaccine to protect against diarrhoea caused by a virus named "rotavirus". Rotavirus is the leading cause of severe diarrhoea among young children. Rotavirus diarrhoea can require hospitalisation of infants and young children and is a frequent cause of childhood death in developing countries. The rotavirus vaccine is approved for use in Malawi but it is not part of the national programme of vaccination.

3. What benefit will my child get if I allow him/her to participate in this study?

If the vaccine is efficacious in this population, infants who receive the vaccine may have the benefit of being protected against rotavirus disease. Infants who receive a placebo will not have this benefit, however if this vaccine proves to be useful, your child's participation will benefit other children in the future.

There will be no charge for study-related doctor visits, examinations and laboratory tests.

At Visit 1 you will be given a health passport for your child and 8 nappies to assist with the collection of stool samples and a bed net will be offered to you. At every study visit you will be provided with a bar of soap for washing your hands after the collection of stool samples. At Visits 1 and 4 you will receive a pen to complete the diary cards. Multi-vitamin syrup for your child will be provided at Visits 3, 4, 5 and 6.

4. What are the possible risks/Inconveniences for my child?

This vaccine will **not cause** diarrhoea but may cause some mild side effects such as irritability (fussiness) and loss of appetite. The other EPI vaccines may cause side effects including pain high fever, and / or crying and swelling at the injection site.

We will take blood samples from your child for testing for HIV (only if you accept) and also to test how well your child's body responded to the new vaccine. This may be painful for the baby and may cause some bruising around the areas where the blood sample was taken. It is, however, not a dangerous procedure.

5. What requirements must the babies fulfil to participate?

They must be healthy babies who are 5-10 weeks of age. They must not have received the usual 6 weeks' EPI vaccines.

After receiving the complete information about the study, you will have the option of either declining or approving your child's participation before he/she may take part.

6. What are the study procedures that my child will go through once I agree to participate?

The participants shall come to …… where:

- Your child will have five study visits (Visits 1, 2, 3, 4 and 6). The study staff will inform you if your child will have one additional visit (Visit 5) and/or needs a contact.
- After being checked by the doctor at 6, 10 and 14 weeks of age (Visits 1, 2 and 3), your child will receive the study vaccine or placebo orally and the usual EPI vaccines.
- At the first visit, a blood sample will be taken from some children. Your child may be one of them. At the 4th visit the doctor will take a blood sample from all children, including your child. These blood samples will be used to test how well your child's body responded to the new vaccine.
- When your child has diarrhoea, we will ask you to make daily notes of some symptoms until the diarrhoea episode has ended in a card provided to you.
- When your child has diarrhoea, we will ask you to collect a stool sample from your child and either contact your Health Surveillance Assistant to pick up the sample or bring the sample to the centre, within 24 hours of collection.
- Testing for HIV will be offered and ideally performed for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4. Pre-test counselling will be offered to you and you may refuse the HIV testing of your child. If you agree to the HIV testing, the doctor will take a blood sample from your child the doctor may take a second blood sample from your child at the following visit if a confirmatory HIV test is needed. If your child is tested and found to be HIV exposed, the study staff will facilitate access to cotrimoxazole prophylaxis at the health centre. At study end, your child will be referred to the cotrimoxazole service provided by the Ministry of Health. If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.
- If your child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised and any HIV testing has not yet been performed, HIV testing, counselling and the concerned Informed Consent will be proposed to you in the hospital. If HIV testing is performed in the hospital, the test will not be repeated at Visit 4. A confirmatory HIV test will be performed as necessary.
- You will be visited once a week by one of our Health Surveillance Assistants who will assist/advise you with any problems you may have.
- The study is expected to end when your baby will be one year old.

7. How can I have my child participate?

If you are interested in your child participating in the study or you require more information, please go to the study nurse or doctor.

CONFIDENTIAL

8. Confidentiality

Your personal details will be taken to allow the study personnel to contact you in order to explain the study to you in more detail. Only people working on the study will have access to the personal and clinical information about your child. They will also need to access your child's clinical records at the hospital where he/she is admitted in the case of illness requiring hospitalisation during the period of the study.

9. Who to contact for clarity and more information

You can also contact us by the following telephone numbers: ……, however if you want to talk to an independent person you can contact: Chairperson of the [redacted]

10. Voluntary participation

Participation is voluntary, you will not be paid to participate, but will get money to cover your transport costs for planned trial visits. There will be no charge for study-related doctor visits, examinations and laboratory tests. You are also free to discontinue participating at any time and this will not affect the services you normally get at the public health facilities.

GSK Biologicals' HRV vaccine (Rotarix™) is approved for use in Malawi and may become available in the private market at a later stage.

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR HIV TESTING OF SUBJECTS IN MALAWI

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 6 (Malawi-specific version) **Date:** 03/08/2006

Company Name: GlaxoSmithKline Biologicals

Subject Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

In order to best evaluate the response to the vaccine, HIV (human immunodeficiency virus) testing of all infants participating in this research study of the HRV vaccine should be ideally performed.

Testing for HIV will be offered and ideally performed for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4.

Should you agree to the test, you will be given pre-test counselling and then a blood sample (± 1ml which is a bit less than a quarter teaspoon) will be taken from your child to perform the HIV test. This will be done by a heel prick. You will be informed of the test results at the following visit and post-test counselling will be offered. If necessary, a blood sample (± 1ml which is a bit less than a quarter teaspoon) will be taken from your child for a confirmatory HIV test. This will be done by a heel prick. At visit 1, this will be done by a heel prick, unless your child is part of the one in ten infants already having blood taken from an arm vein. At visit 4 your child will not require an additional needle prick for HIV testing as blood will already be taken from an arm vein at this visit. Depending on when the HIV test is done and whether a confirmatory HIV test is done, your child may have an additional visit (Visit 5 approximately two weeks after Visit 4) and/or contact.

You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study.

If your child develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised and any HIV testing has not yet been performed, HIV testing,

counselling and the concerned Informed Consent will be proposed to you in the hospital. If HIV testing is performed in the hospital, the test will not be repeated at Visit 4. A confirmatory HIV test will be performed as necessary.

If your child is tested and found to be HIV exposed and/or HIV positive, the study staff will provide cotrimoxazole prophylaxis for the duration of study follow-up. At study end, your child will be referred to the cotrimoxazole service provided by the Ministry of Health. If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.

CONFIDENTIAL Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification 102248 (rota-037)

Consent statement

The aims and procedures of the HIV testing have been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Informed Consent for HIV testing, Version 3 (Malawi-specific version 6), dated 03/08/2006, 5 pages].

I, ,the parent / legal guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child (subject)

hereby freely give my consent for my child to undergo HIV testing.

I confirm that I have had the opportunity to ask questions about this HIV testing and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child to take part in this HIV testing.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any questions related to my child's HIV testing during the study, or if I do not want to receive my child's HIV test result.

CONFIDENTIAL

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification 102248 (rota-037)

Consent statement

***Signature (or thumb-print) of Parent / Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

***Printed name of Parent / Legal Guardian** _____

If the parent/legal guardian is illiterate, an Independent Literate Witness should also sign the consent form

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

CONFIDENTIAL Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification 102248 (rota-037)

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the aims and procedures of the HIV testing to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR SECOND YEAR FOLLOW-UP OF SUBJECTS

Study Identification: 102248 (Rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 1 Malawi-specific version **Date:** 03/08/2007

Company Name: GlaxoSmithKline Biologicals

Subject Identification:

Healthy infants who were 5-10 weeks of age at the time of the first vaccine/placebo dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Dear Parent or Guardian:

Your child is part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals. Your child has received three doses of the rotavirus vaccine or its placebo by mouth, approximately four weeks apart.

Your child was planned to be followed until 12 months of age. However, as the study period has been extended, we would like to continue the follow-up of your child until he/she is between 18 and 24 months of age (Visit 7). The maximum duration of follow-up will be 24 months. This would allow us to find out if the vaccine continues to protect young children against severe diarrhoea caused by the rotavirus during the second year of life and monitor your child to see if they get any other problems or illnesses during this year.

Your decision to let your child participate in the extra year of follow-up is voluntary and you are free to change your decision to continue in the study at any time. If you wish to leave the study at any time please let any member of the study staff know.

No additional blood samples will be taken from your child during the second year follow-up period to evaluate the rotavirus vaccine. HIV testing will be offered by the study if needed according to the HIV-testing program in Malawi or where there is a clinical indication. This HIV testing is voluntary.

The study staff will review with you the study procedures for the second year of follow-up during Visit 6. The procedures are similar to the period in the first year from Visit 4 to Visit 6. During the study, a member of the study staff will visit you weekly to check if your child had any diarrhoea and to assist/advise you with any other problems your child

may have. The study procedures at Visit 6 (when your child is one year of age) and Visit 7 (when your child is between 18 and 24 months of age) are summarised below:

At Visit 6,

- A 'GE diary card' will be provided to you and should be used to record information during any GE episode experienced by your child between Visit 6 and Visit 7. If needed the HSA will help you to complete the diary card during the weekly visits. You should return the completed diary cards to the HSA at the next home visit or bring it to the study clinic, at which time you will be provided with a new 'GE diary card'.
- A stool sample bottle will be provided to you at Visit 6. You should collect a single stool sample from your child during any GE episode and return the stool sample to the investigator as soon as possible after collection either by giving it to the HSA during a home visit or bringing it to the study clinic at which time you will be provided with a new stool sample bottle. If there are 5 or more GE-free days between episodes of GE then please provide a single stool sample for each episode.

At Visit 7,

- Visit 7 will be the final visit.
- Your child will be examined by the study clinician.
- You will be asked by the investigator if your child has been sick, had any episodes of GE or was hospitalised since the previous visit.
- You will return the completed diary cards which have not previously been handed in to the study staff.
- Study conclusion.

To help with the time and travel expenses, you will be reimbursed MK300 for each scheduled study visit completed by your child.

If during the study period you are concerned about your baby's health the study clinicians will be available to assess your child during office hours and offer advice and treatment. There will be no charge for these visits. Out of hours please attend your local hospital if you have concerns. If this occurs please inform a member of study staff in the following days.

- If your child develops symptoms during the study period, indicative of AIDS or has to be hospitalised and HIV testing has not yet been performed, HIV testing will be proposed to you at the local clinic or, in the case of hospitalisation, during hospital admission.

The names of people who can be contacted for information on the trial and/or medical care

If you require any additional information concerning the availability of medical care, if you think your child has experienced a research-related illness or injury or if you have

any questions concerning the study please contact one of the study clinical staff members detailed below.

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Consent statement

The procedures of the second year follow-up have been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Written Informed Consent for 2nd year follow-up (Version 1 Malawi-specific version), dated 03/08/2007, 6 pages].

I, ,the parent / legal guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child (subject)

hereby freely give my consent for my child to participate in the 2nd year follow-up.

I confirm that I have had the opportunity to ask questions about the 2nd year follow-up and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child to take part in the 2nd year follow-up.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any questions related to my child's participation in the 2nd year follow-up during the study or if I want to withdraw my child from the study.

Tick as appropriate

I give permission that any stool samples from my child are stored for up to 15 years for the purpose of further testing for the disease and vaccine under study or for the quality assurance of laboratory tests, excluding genetic research.

I do not give permission that any stool samples from my child are stored for up to 15 years.

Consent statement

***Signature (or thumb-print) of Parent / Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

Printed name of Parent / Legal Guardian _____

***If the parent/legal guardian is illiterate, an Independent Literate Witness should sign the consent form**

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Statement by Doctor or designated person who conducted the informed consent discussion:

I have carefully explained the aims and procedures regarding the 2nd year follow-up to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR HIV TESTING IN SECOND YEAR OF FOLLOW-UP

Study Identification: 102248 (Rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 1 Malawi-specific version **Date:** 03/08/2007

Company Name: GlaxoSmithKline Biologicals

Subject Identification:

Healthy infants who were 5-10 weeks of age at the time of the first vaccine/placebo dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Dear Parent or Guardian:

Your child is part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals. Your child/ has received the rotavirus vaccine or its placebo three times by mouth.

In the second year of follow-up, there is no routine HIV testing proposed as part of the rotavirus vaccine study. However in special circumstances we offer individual children the opportunity to be tested.

1. Three Months Post Breastfeeding Cessation

National Guidelines in Malawi recommend repeat HIV testing 3 months after cessation of breast feeding, in children who have been exposed to the HIV virus so that children can be given appropriate treatment.

2. Clinical Need for HIV Testing

If your child develops symptoms during the study period, indicative of AIDS or has to be hospitalised and HIV testing has not yet been performed, HIV testing will be proposed to you at the local clinic or, in the case of hospitalisation, during hospital admission.

We feel your child has an indication for HIV testing and would like to carry out this test. This will involve a blood sample (+/- 1ml which is a bit less than a quarter of a teaspoon) taken either by heel prick or from the arm in the same way that the sample was collected at Visit 4.

You have the choice to refuse the test. If you refuse the test, your child can continue to participate in the study.

If an HIV test is performed and you agree, we would like to record the result in the Case Report Form (a document used by the investigator to record all the data pertaining to a subject) to use in our research analysis. All the relevant information regarding your child will be kept confidential.

- ☐ I agree that the results of any HIV tests performed during the period of follow-up can be recorded in my child's Case Report Form.
- ☐ I do not agree that the results of any HIV tests performed during the period of follow-up can be recorded in my child's Case Report Form.

If you decide not to allow us to include the data for research analysis, we will still perform the HIV testing because of the clinical needs of your child.

If your child is tested and found to be HIV positive, the study staff will provide you with cotrimoxazole prophylaxis for the duration of study follow-up. At study end your child will be referred to the cotrimoxazole service provided by the Ministry of Health. If your child is tested and found to be HIV positive, the study staff where clinically indicated will facilitate access to a HIV staging facility and /or ARV treatment centre.

If you have any questions, please contact the site staff the details mentioned below:

Name of study staff:

Address of study staff:

Telephone number of study staff:

Fax number of study staff:

Consent statement

The aims and procedures of the HIV testing have been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Written Informed Consent Form for HIV testing in 2nd year of follow-up, (Version 1 Malawi-specific version), dated 03/08/2007, 5 pages]

I, ,the parent / legal guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child (subject)

hereby freely give my consent for my child to undergo HIV testing

I confirm that I have had the opportunity to ask questions and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child to undergo HIV testing

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case I have any questions on this.

Study Identification 102248 (Rota-037) **CONFIDENTIAL** Subject ID_____
Supplementary Written Informed Consent Form for HIV testing in 2nd year of follow-up

Consent statement

***Signature(or thumb-print) of Parent / Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

Printed name of Parent / Legal Guardian_____

***If the parent/legal guardian is illiterate, an Independent Literate Witness should sign the consent form**

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Study Identification 102248 (Rota-037) **CONFIDENTIAL** Subject ID_____
Supplementary Written Informed Consent Form for HIV testing in 2nd year of follow-up

Statement by Doctor or designated person who conducted the informed consent discussion:

I have carefully explained the aims and procedures of the HIV testing to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

WRITTEN INFORMED CONSENT FORM FOR SUBJECTS IN SOUTH AFRICA COHORT 2

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Simplified Study Title: A study to find out if the vaccine protects against diarrhoea and if 2 doses of the HRV vaccine are as good as 3 doses in their ability to protect against diarrhoea caused by rotavirus, and to determine if they are safe when this vaccine is given with routine childhood vaccinations in healthy infants.

Version Number: 11 South Africa-specific version **Date:** 04/08/2006

Company Name: GlaxoSmithKline Biologicals

Subject Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Purpose/Description/Procedures/Duration

Rotavirus is a leading cause of severe diarrhoea among children. GSK Biologicals, a drug company that tests new vaccines and drugs has developed a new vaccine- the human rotavirus vaccine (referred to as HRV vaccine), for protection of children from developing this type of diarrhoea. The purpose of this research is to find out if the vaccine protects against diarrhoea and if 2 doses of this new vaccine are as good as 3 doses, both in terms of providing protection and in being safe. The vaccine that is being tested has to be taken by mouth, (like the polio drops). We wish to invite your child/ward to take part in this research study.

The main objective of this document, called a consent form, is to provide you as the parents or guardians of a child/ward with information necessary to help you make the decision about whether or not to have your child/ward in this study. The document provides information about the vaccine including the likely advantages and disadvantages

associated with the vaccine, the study purpose and the study procedures. This document also tells you about your rights and responsibilities on behalf of your child/ward if you decide to enrol him/her in the study as a participant

This consent form may contain words that you do not understand. Please ask the study doctor or staff to explain anything unfamiliar, and to answer any questions that you have about the study.

In order to help you in understanding this study; you will receive a 3-page summary of this consent form.

You will be asked to complete an Informed Consent Feedback Form. Your answers to the questions in this form will allow the person taking informed consent to understand if there are any points that you did not understand. In that case, the informed consent will be again explained to you.

Once you understand the study, you will be asked if you want your child/ward to be in the study. If you do, you will be asked to sign this form.

The study doctor and/or the institution are paid to conduct this research study by two international organisations: the World Health Organisation (WHO) and the Program for Appropriate Technology in Health (PATH). GlaxoSmithKline Biologicals (GSK) is responsible for administration of the study including clinical trial supply management, clinical data collection, analysis and biological samples analysis.

This medical research study will be conducted on 5670 infants coming for their routine immunisation visits to the study centers in Malawi and South Africa. All healthy infants between the ages of 5-10 weeks can take part in this study.

All children participating in this study will have five study visits (Visits 1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) and/or contact depending on if and when the HIV test is done and whether a confirmatory HIV test is done. During the study, a member of the study staff will visit you at home weekly.

The main purpose of this study is to find out how well the HRV vaccine works to prevent severe cases of rotavirus diarrhoea. This will be done by giving some children the HRV vaccine and some children a placebo (product that looks like the real vaccine, but does not contain any active ingredient), and comparing the results. We will take stool samples from each child with diarrhoea for testing to find the number of rotavirus diarrhoea cases. This will allow us to assess the effectiveness of the HRV vaccine (ability to prevent rotavirus diarrhoea). We will also look for any serious side effects to evaluate safety of HRV vaccine. A blood sample (± 2 ml which is a bit less than half teaspoon) will be taken from all children at Visit 4 to see how your child's/ward's immune system (part of body that fights infection) reacts to the vaccines.

According to the national guidelines in South Africa, HIV (human immunodeficiency virus) testing of all infants should be ideally performed during the study. Testing for HIV

will be offered for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4. You have the choice to refuse the test. If you refuse the test, your child/ward will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling, you will be asked to sign a separate consent form to allow HIV testing and then a blood sample (± 3 ml which is a bit more than a half teaspoon) will be taken from your child/ward to perform the HIV test. You will be informed of the test results at the following visit and post-test counselling will be offered. If necessary, a blood sample (± 2 ml which is a bit less than a half teaspoon) will be taken from your child/ward for a confirmatory HIV test. Depending on when the HIV test is done and whether a confirmatory HIV test is done, your child/ward may have one additional visit (Visit 5) and/or contact so that the study staff can inform you of the HIV test results and offer further counselling. The study staff will inform you if your child/ward will require an additional visit and/or contact.

If your child/ward is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.

Cotrimoxazole prophylaxis will be prescribed for all infants who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or Prevention of Mother To Child Transmission (PMTCT) programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If your child/ward is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centres to which he/she has been referred. If your child/ward is HIV negative and still HIV exposed (due to breast feeding), he/she will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

Ethical and Regulatory Approval

This clinical study protocol has been submitted to: 1) [redacted] 2 [redacted] South Africa, 3) [redacted] South Africa, 4) [redacted] South Africa [redacted] 5) [redacted] Switzerland. These committees have granted written approval.

The study has been structured in accordance with the 2004 version of Declaration of Helsinki, which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained should you wish to review it.

Study Participation

The duration of this study is for a maximum period of 10 to 11 months. All children participating in this study may have five study visits (Visits 1, 2, 3, 4 and 6). The study staff will inform you if your child/ward will have one additional visit (Visit 5) and/or contact depending on when the HIV test is done and whether a confirmatory HIV test is done.

During the study, a member of the study staff will visit you weekly to assist/advise you with any problems you may have.

If you are interested to take part in the research, the research staff will ask you questions about your child's/ward's medical history and the medicines that your child/ward may be taking. Your child/ward will not be able to participate in the study if she or he is taking certain kinds of medicines or has certain specific illnesses.

In this study one third of the children will get 3 doses of vaccine, another third will get 2 doses of vaccine and one dose of placebo (an inactive product that looks like the vaccine but has no effect on the body), and the remaining third will get 3 doses of placebo. Randomisation will be used to assign children to one of the three treatment groups. Randomisation means that the participants are put into a group by chance. It is like flipping a coin. Your child/ward will have a 2 out of 3 chance of receiving the HRV vaccine (either three doses of HRV vaccine or two doses of HRV vaccine and one dose of placebo) and a 1 out of 3 chance of receiving a placebo (looks like vaccine but has no activity). Neither you nor your doctor will know whether your child/ward receives the real vaccine or the inactive liquid. If needed in case of emergencies, however, the doctor will be given this information. We need to give inactive placebo to some children to make sure that the effect we see after our research has not occurred because of chance, but occurred because of the vaccine. This is the way that scientific studies are designed.

If your child/ward is eligible to take part in the trial, he/she will receive three doses given four weeks apart. The study vaccine or placebo will be given by mouth. All study participants will be observed closely for at least 30 minutes following the administration of vaccines to monitor any reaction to the vaccine/placebo. As mentioned before, neither the doctor nor you will know what your child/ward has received, but your child/ward will be followed up very carefully to make sure that he gets medical attention when required.

Your child/ward will receive his/her nationally recommended routine vaccinations at the same time of the administration of the study vaccine dose. This study in no way alters the routine immunisation schedule, and it is very important for you to follow the recommendations given by the immunisation nurse or Care Group Leader.

The study is expected to end when your baby will be one year old. The study procedures are summarised below. The study nurse will review all the study procedures with you in detail.

- At Visits 1, 2 and 3 that will take place four weeks apart, the doctor will examine each child and give a dose of HRV or its placebo by mouth. At each of these visits, you will receive two diary cards to collect information on diarrhoea and information on any medicines that your child/ward has received. The study staff will train you on how to complete these diary cards.
- Each child will also receive all the routine vaccines at Visits 1, 2 and 3. For other routine vaccinations (at 9 months of age), you will be requested to take your child/ward to your local clinic.
- Visits 4, 5 and 6 are follow-up visits.
    - Visit 4 will take place one month after Visit 3.
    - Visit 5 may only take place if your child/ward had an HIV test at Visit 4. The HIV test results will be communicated to you at this visit and blood sample for confirmatory HIV test will be taken if necessary. The study staff will inform you if a contact is needed so that results of the confirmatory HIV test can be communicated to you. There will no other study procedures.
    - Visit 6 will be the final visit and will take place when your child/ward is one year old.
- At each visit, the investigator will ask you if your child/ward has been sick or hospitalised since the previous visit.
- A blood sample (± 2 ml which is a bit less than half a teaspoon) will be collected from the most convenient and safe site, most probably from an arm vein, from all infants, including your child/ward, at Visit 4. This blood sample will be tested to measure the amount of substance in the blood that fights infection (called antibodies). This will allow the researchers to see how your child/ward reacts to the vaccines to fight infection (called immune response).
- According to the national guidelines in South Africa, HIV (human immunodeficiency virus) testing of all infants should be ideally performed during the study. Testing for HIV will be offered for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4. You have the choice to refuse the test. If you refuse the test, your child/ward will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling, you will be asked to sign a separate consent form to allow HIV testing and then a blood sample (± 3 ml which is a bit more than a half teaspoon) will be taken from your child/ward to perform the HIV test. You will be informed of the test results at the following visit and post-test counselling will be offered. If necessary, a blood sample (± 2 ml which is a bit less than half teaspoon) will be taken from your child/ward at the following visit for a confirmatory HIV test. If your child/ward has the initial HIV testing at Visit 4, he/she will have one additional visit (Visit 5 at 21-

48 days after Visit 4) to communicate results of the initial HIV test to you and perform confirmatory HIV test if required. A contact will be planned in 2 weeks after Visit 5 to inform you about the confirmatory HIV test result and offer further counselling.

- During the entire study period (from Visit 1 up until Visit 6), if your child/ward develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed to you at the site or, in the case of hospitalisation, at hospital admission if possible. A confirmatory HIV test will be performed as necessary.
- If your child/ward is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.
- Cotrimoxazole prophylaxis will be prescribed for all infants who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If your child/ward is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centres to which he/she has been referred. If your child/ward is HIV negative and still HIV exposed (due to breast feeding), he/she will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.
- At the first visit, you will receive a Trial Identification Card, which will specify details of the trial, 24-hour telephone number of the study doctor, study nurses and study staff.
- During the study, a member of the study staff will visit you weekly to check if your child/ward had any diarrhoea. Each home visit will take about half an hour.
- If you feel that your child/ward has symptoms of severe diarrhoea, you should take him/her to the nearest hospital/medical facility. The hospital/medical facility that is currently nearest to you is: _____. You should show the Trial Identification Card to any health care professional that you consult.
- You should contact your health care practitioner at your health center immediately should your child/ward manifest any signs or symptoms that you perceive as serious. The study staff will be available to your health care practitioner from the nearest health center for consultation for the entire study period (24 hours/day).

- When your child/ward has diarrhoea, you will be asked to complete a Diary Card daily until end of diarrhoea. The information requested on the Diary Cards includes taking your child's/ward's temperature and noting information on the diarrhoea episode. The study staff member will help you to complete the diary card during the weekly visits.
- You will be asked to take stool samples from your child/ward if he/she develops diarrhoea at any time from Visit 1 to Visit 6. Containers for collection of stool samples will be provided to you. You will be asked to either contact your Care Group Leader to pick up the sample or bring the sample to the centre, within 24 hours of collection.
- A part of the collected stool sample will be stored as back-up of specimens in case of loss during shipment.
- If you agree, collected samples may be stored for up to 15 years for further testing for the disease under study (no genetic testing).
- Collected samples may undergo additional testing to further evaluate the immunogenicity of the vaccine as needed.

Your responsibilities are:

- to follow the instructions given by the study doctor and the study staff,
- to stay in the same area for the coming year,
- to bring your child/ward to the clinic at scheduled visits and to answer the final questions at the end of the study,
- to take a stool sample from your child/ward if he/she has diarrhoea and either contact your Care Group Leader to pick up the sample or bring the sample to the centre, within 24 hours of collection,
- to complete the information requested on the Diary Cards which includes taking your child's/ward's temperature and noting information on the diarrhoea episode and information on any medicine that your child/ward has received,
- to promptly report to the study staff should your child/ward develop an illness that you perceive as serious or undergo hospitalisation.

If you want to stop your child's/ward's participation in the study or if you find you have not followed instructions listed above, it is important that you notify the study doctor or study staff.

Number of Subjects

This study will involve a total of approximately 5670 infants at several sites in Malawi and South Africa. A minimum of 2,600 subjects will be enrolled in South Africa and a maximum of 3070 subjects will be enrolled in Malawi.

Recruitment of new participants in this study will stop when the planned number of participants has been achieved.

The names of people who can be contacted for information on the trial and/or medical care

The physician you can contact if you require any additional information or have any questions concerning the trial, availability of medical care or if you think you have experienced a research-related illness or injury.

You may ask questions about the study. If you have any questions, please contact:

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Fax number of investigator:

Risks/Inconveniences

Over 80,000 adults, children, and infants have participated in studies with the rotavirus vaccine. During these studies, over 37,000 infants received at least one dose of the vaccine.

The rotavirus vaccine caused only mild side effects in some infants that were similar to those observed in infants who were given a placebo (product that looks like the real vaccine, but does not contain any active ingredient). The occurrence of irritability (fussiness) and loss of appetite were reported in more than 1 in 10 subjects. The following reactions were commonly (less than 1 in 10 subjects) reported: fever, fatigue, diarrhea, vomiting, flatulence (excessive gas), abdominal pain and regurgitation of food (bring back already swallowed food). The following were uncommonly (less than 1 in 100 subjects) or some even rarely reported (less than 1 in 1000): crying, sleep disorder, somnolence (sleepiness) and constipation, upper respiratory tract infection, hoarseness, rhinorrhoea (runny nose), dermatitis (inflammation of the skin), rash and muscle cramp.

The vaccine will not cause the rotavirus disease.

Seven years ago, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage of the small intestine that requires immediate attention by a doctor. If intussusception is recognised early, treatment can be given for complete recovery. Because RotaShield™ may have increased the risk of intussusception, it is no longer available. If you are interested, your doctor can give you more information on intussusception.

The rotavirus vaccine used in this study was tested in a large study with 63,225 children and results showed that this rotavirus vaccine being tested in this study does not increase the risk of intussusception.

There may be momentary, mild discomfort and bruising of the skin on the arm 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 or haemoglobin that may be caused due to loss of blood).

Your child/ward will receive routine vaccinations (DTPw-HBV/Hib and OPV) during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, or crying.

As with any experimental vaccine, unexpected serious adverse experiences, including allergic reactions to the vaccine, may occur. All the medical equipment to treat any serious reactions to the study vaccine will be available.

You should contact the study contact person at your health center immediately should your child/ward show any reactions that you are worried about.

You will be informed of any new findings developed during the course of this research study.

Benefits

If the vaccine is efficacious in this population, infants who receive the vaccine may have the benefit of being protected against rotavirus diseases. Infants who receive a placebo will not have this benefit, however if this vaccine proves to be useful, your child's/ward's participation will benefit other children in the future.

If your child/ward is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study.

Cotrimoxazole prophylaxis will be prescribed for all infants who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If your child/ward is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centres to which he/she has been referred. If your child/ward is HIV negative and still HIV exposed (due to breast feeding), he/she will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

Alternative Treatment/Measure of Prevention

GSK Biologicals' HRV vaccine (Rotarix™) is approved for use in South Africa and is available in the market.

Disease caused by rotavirus is treated with oral rehydration solutions or if necessary, intravenous fluid replacement. This is to prevent dehydration and shock. There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Joining this study is voluntary. If you decide against joining, there will be no penalty and your child/ward will receive the routine vaccinations, as normal, by the health care centre. You and your child/ward will lose no benefits to which you are otherwise entitled.

Compensation for Study-Related Injury

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that the sponsor, GlaxoSmithKline without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for the study. GlaxoSmithKline will not compensate you for any procedure carried out which is not in accordance with the protocol for the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. A copy of the guidelines for compensation for a possible injury/disablement that occurs while taking part in this study can be obtained from your doctor.

Payment to Subjects

You will receive no payment for your child's/ward's participation in this study.

Expenses/Costs

To help with the time and travel expenses, you will be reimbursed R150.00 for each scheduled study visit completed by your child/ward. There will be no charge for study-related doctor visits, examinations, and laboratory tests. All study vaccines will be provided free of charge.

If your child/ward is referred to a HIV staging facility and/or ARV treatment centres during the study, transport will be offered through the study project or you will be given R40.00 to cover public transport costs to and from the ARV treatment site.

Right to ask questions and/or withdraw from the study

If you want any information regarding your child's/ward's rights as a research participant, or complaints regarding this research study, you may contact anyone of these independent committees established to help protect the rights of research participants.

Name of the Chairperson of Ethics Committee: _____

Name of the Ethics Committee**:**

Address of Ethics Committee:

Tel:

Fax:

If you have any questions about this trial you should first discuss them with your doctor or the ethics committee. After you have contacted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar
SA Medicine Control Council
Department of Health
Private Bag X828 PRETORIA 0001

Personal Doctor / Specialist option

Please indicate below, whether you want me to notify your child's/ward's personal doctor or your child/ward's specialist of their participation in this study:

☐ YES, I want you to inform my child's/ward's personal doctor/specialist of their participation in this study.

☐ NO, I do not want you to inform my child's/ward's personal doctor/specialist of their participation in this study.

☐ My child/ward does not have a personal doctor/specialist.

Termination of Subjects' Study Participation

Your child's/ward's participation in the study may be stopped for any of the following reasons:

- If you do not follow the study doctor's instructions,
- The study doctor decides it is in the best interest of your child's/ward's health and welfare to discontinue participation in the study,

- There are either not enough subjects interested in participating in the study or the study has reached the required number of subjects,
- GSK Biologicals has decided to stop the study at this site for other reasons not known at this time,
- GSK Biologicals stops enrolling new subjects into study for any reason, and your child/ward is in the screening phase of the study and has not yet been assigned to one of the vaccine groups.

Voluntary Participation and Subjects Right to End Participation

Your child's/ward's participation in this study is voluntary. If you do decide for your child/ward to take part, you will be given this information to keep and be asked to sign this consent form. 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. You must inform your study doctor if you decide to do this. 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.

Any information and results collected before your child's/ward's withdrawal from the study will be used by GlaxoSmithKline.

Confidentiality and Data Privacy

Maintaining confidentiality is important to GlaxoSmithKline Biologicals, WHO and PATH. Your child's/ward's personal information (for example, gender, age, the details of his/her medical conditions) and other information (the data collected by GlaxoSmithKline Biologicals as part of the study) will be identified by a number (i.e., coded). Your child's/ward's name will not appear in any publications or reports produced from this study.

GlaxoSmithKline Biologicals will keep the information and the results collected about your child/ward in this study. Your child's/ward's name and address are not included in the information kept by GlaxoSmithKline Biologicals - only your study doctor will keep this information. GlaxoSmithKline Biologicals has told your study doctor to keep the information about your child/ward in a secure place. GlaxoSmithKline Biologicals will comply with internal procedures to protect personal and other information even in countries where data privacy laws are less strict than in Europe/US.

By agreeing to take part in this research study you will be allowing certain persons to see the information about your child/ward (both personal, including his/her name, and other information) held by the study doctor. Your child's/ward's information will be looked at to confirm that it is correct and that it is related to your child/ward. This will be done by selected people working for GlaxoSmithKline and organisations acting on behalf of GlaxoSmithKline Biologicals S. A., [redacted]

[redacted] and [redacted] along with the government regulatory authorities. These persons are required to maintain the confidentiality of your information.

The study doctor or designated study staff will also need to access your child's/ward's clinical records at the hospital where he/she is admitted in the case of illness requiring hospitalisation during the period of the study.

Your child's/ward's information will be processed electronically (i.e., by a computer) or manually and analysed to determine outcome of this study. GlaxoSmithKline Biologicals may use your child's/ward's information for other medical/health care purposes related to development of this vaccine. For this purpose only your child's/ward's coded information will be used.

Your child's/ward's information may be sent to regulatory authorities, to the IEC/IRB, to other doctors and/or organisations working with GlaxoSmithKline Biologicals. It may also be sent to other GlaxoSmithKline Biologicals sites in this country and in other countries where there may be different or lesser standards for looking after it. GlaxoSmithKline Biologicals will apply the same standard in the protection of your information to the extent permitted by law.

You have the right to ask the study doctor about the data being collected on your child/ward for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your child's/ward's personal information and to have any needed corrections to it made.

Future Use of Leftover Blood and/or Stool Samples

If you agree, collected blood and/or stool samples may be stored for up to 15 years and used for purposes related to testing for the disease under study and the quality assurance of laboratory tests. This may include the set up of new test methods as well as making sure that new tests are comparable to previous methods and work reliably. No genetic testing will be performed.
Samples will not be labelled with information that directly identifies you but will be coded with your study subject number.

Notification of New Information

Sometimes during the course of a research project, new information becomes available about the vaccine that is being studied. If this happens, we will tell you about new information that may affect you and your child/ward willingness to stay in this study.

Consent statement

The HUMAN ROTAVIRUS vaccine study 102248 (Rota-037) has been clearly explained to me and I have read and understood the information provided [Written Informed Consent Form, Version number 11 South Africa-specific version, dated 04/08/2006, 18 pages].

I, , the Parent/Legal Guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child/ward (subject)

hereby freely give my consent for my child/ward to take part in this vaccine study.

I 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.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child/ward to take part in this study.

I agree to take part in this study and to my child's/ward's participation in this study. I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any study-related questions during the study, or if I want to withdraw my child/ward from the study.

> I give permission that the samples from my child are stored for up to 15 years for the purpose of further testing for the disease and vaccine under study or for quality assurance of laboratory tests, excluding genetic research.
>
> I do not give permission that the samples from my child are stored for up to 15 years.

Consent statement

***Signature (or thumb-print) of Parent/Legal Guardian** _____ **Date:** _____
DD/ MM/ YY

***Printed name of Parent/Legal Guardian** _____

If the parent/legal guardian is illiterate, an Independent Literate Witness should also sign the consent form.

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Statement by Doctor or designated person who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

Subject number _____

INFORMED CONSENT FEEDBACK FORM

This Informed Consent Feedback form will allow the person taking your consent to understand if there are any points of the Informed Consent (IC) you did not understand. In that case, the IC will be explained to you again.

Please may we ask you to take a few minutes of your time to complete this Informed Consent Feedback form? We would like you to choose the answer which you think is the MOST correct answer for each of the questions.

1) ***What does the rotavirus vaccine protect against?***

- ☐ **HIV/AIDS**
- ☐ **Diarrhoea caused by rotavirus**

2) ***Will your child receive the RV vaccine or a placebo?***

- ☐ **RV vaccine**
- ☐ **Placebo**
- ☐ **Either RV vaccine or Placebo**

3) ***How many visits (not counting this visit) will your child have to return for during the study at the most*****?**

- ☐ **2**
- ☐ **3**
- ☐ **5**

4) ***For how long will your child be followed up during the study?***

- ☐ **3 months**
- ☐ **6 months**
- ☐ **until 1 year old**

5) ***What is a diarrhoea event in the study?***

- ☐ **Having 1 looser than normal stool per day**
- ☐ **Having 2 looser than normal stools per day**
- ☐ **Having 3 or more looser than normal stools per day**

6) ***In case your child has an episode of diarrhoea, you should collect a stool sample and complete a diary card?***

Subject number _____

☐ **True**

☐ **False**

7) ***Blood samples will be collected from your child?***

☐ **True**

☐ **False**

8) ***If you agree to participate in the study now, you can refuse HIV testing for your child at any time?***

☐ **True**

☐ **False**

9) ***If your child is tested and found to be HIV positive and needs to be sent to ARV centers, the study staff will assist you to go to such a place?***

☐ **True**

☐ **False**

10) ***In addition to the study vaccine, you will get the routine EPI vaccinations at the Health Centre***

☐ **True**

☐ **False**

11) ***How often will the Care Group Leader (CGL) come to visit your child during the study?***

☐ **Once, every week**

☐ **Once, every month**

12) ***You must carry the orange trial identification card at all times and show it to the doctor when you go to the clinic or hospital?***

☐ **True**

☐ **False**

13) ***In case of severe diarrhoea or any serious illness, you should go to the nearest hospital, show your trial identification card and inform study staff?***

☐ **True**

☐ **False**

Informed Consent Feedback Form: South Africa Cohort 2 Study Identification 102248 (Rota-037)

Subject number _____

14) ***You don't have to pay for the doctor's visit at the trial site and sample testing?***

☐ **True**

☐ **False**

15) ***This is a voluntary study; you will not receive any money for your child's participation in the study, but will receive a fixed amount of money to help with time and travel expenses for planned study visits.***

☐ **True**

☐ **False**

16) ***Once in the study, you have the right to ask questions at any time?***

☐ **True**

☐ **False**

17) ***You have the right to stop your child's participation in the study?***

☐ **True**

☐ **False**

18) ***Your child's personal information (name or other identifying particulars) will be made publicly available?***

☐ **True**

☐ **False**

Subject's Parent/Legal Guardian name _____

Date: _____

Thank you for taking the time to complete this questionnaire.

Summary Informed Consent Form
Study Identification 102248 (rota-037)

CONFIDENTIAL

Study Rota-037- Information Sheet for subjects in South Africa Cohort 2

1. What is the study about?

This study is about a vaccine against diarrhoeal disease due to rotavirus. In this study, children will be given two or three oral doses of the vaccine or three oral doses of placebo at the same time as the other EPI vaccines given at your local clinic. The placebo is a product that looks like the real vaccine, but does not contain any active ingredient. The placebo is used in studies where the effect of the vaccine has to be evaluated.

The objective of the study is to evaluate if the vaccine will prevent your child from getting rotavirus diarrhoea.

2. What is the vaccine for?

This is a new vaccine to protect against diarrhoea caused by a virus named "rotavirus". Rotavirus is the leading cause of severe diarrhoea among young children. Rotavirus diarrhoea can require hospitalisation of infants and young children and is a frequent cause of childhood death in developing countries. This rotavirus vaccine is approved for use in South Africa and available on the market.

3. What benefit will my child get if I allow him/her to participate in this study?

If the vaccine is efficacious in this population, infants who receive the vaccine may have the benefit of being protected against rotavirus disease. Infants who receive a placebo will not have this benefit, however if this vaccine proves to be useful, your child's participation will benefit other children in the future.

There will be no charge for study-related doctor visits, examinations and laboratory tests.

4. What are the possible risks/Inconveniences for my child?

This vaccine will **not cause** rotavirus disease but may cause some mild side effects such as irritability (fussiness) and loss of appetite. The other EPI vaccines may cause side effects including pain high fever, and / or crying and swelling at the injection site.

We will take blood samples from your child for testing for HIV (only if you give permission to do so) and also to test how well your child's body responded to the new vaccine. This may be painful for the baby and may cause some bruising around the areas where the blood sample was taken. It is, however, not a dangerous procedure.

5. What requirements must the babies fulfil to participate?

They must be healthy babies who are 5-10 weeks of age. They must not have received the usual 6 weeks' EPI vaccines.

After receiving the complete information about the study, you will have the option of either declining or approving your child's participation before he/she may take part.

6. What are the study procedures that my child will go through once I agree to participate?

The participants shall come to …… where:

- Your child will have five study visits (Visits 1, 2, 3, 4 and 6). The study staff will inform you if your child will have one additional visit (Visit 5) and/or needs a contact.
- After being checked by the doctor at 6, 10 and 14 weeks of age (Visits 1, 2 and 3), your child will receive the study vaccine or placebo orally and the usual EPI vaccines.
- At the 4th visit the doctor will take a blood sample from all children, including your child. These blood samples will be used to test how well your child's body responded to the new vaccine.
- When your child has diarrhoea, we will ask you to make daily notes of some symptoms until the diarrhoea episode has ended in a card provided to you.
- When your child has diarrhoea, we will ask you to collect a stool sample from your child and either contact your Care Group Leader to pick up the sample or bring the sample to the centre, within 24 hours of collection.
- Testing for HIV will be offered and ideally performed for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4. Pre-test counselling will be offered to you and you may refuse the HIV testing of your child. If you agree to the HIV testing, the doctor will take a blood sample from your child. The doctor may take a second blood sample from your child at the following visit if a confirmatory HIV test is needed. If your child is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment center during the study. Decisions towards treatment will be taken by appropriate staff at these treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.
- During the entire study period (from Visit 1 up until Visit 6), if your child/ward develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised with any SAE and HIV testing has not yet been performed, HIV testing will be proposed to you at the site or, in the case of hospitalisation, at hospital admission if possible. A confirmatory HIV test will be performed as necessary.
- Cotrimoxazole prophylaxis will be prescribed for all infants who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or Prevention of Mother To Child Transmission (PMTCT) programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PMTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If your child/ward is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centre to which he/she has been referred. If your child/ward is HIV negative and still HIV exposed (due to breast feeding), he/she will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.
- You will be visited once a week by one of our Care Group Leaders who will assist/advise you with any problems you may have.
- The study is expected to end when your baby will be one year old.

7. How can I have my child participate?

If you are interested in your child participating in the study or you require more information, please go to the study nurse or doctor.

8. Confidentiality

Your personal details will be taken to allow the study personnel to contact you in order to explain the study to you in more detail. Only people working on the study will have access to the personal and clinical information about your child. They will also need to access your child's clinical records at the hospital where he/she is admitted in the case of illness requiring hospitalisation during the period of the study.

9. Who to contact for clarity and more information

You can also contact us by the following telephone numbers: ……, however if you want to talk to an independent person you can contact
……

10. Voluntary participation

Participation is voluntary, you will not be paid to participate, but will get money to cover your transport costs for planned trial visits. There will be no charge for study-related doctor visits, examinations and laboratory tests. You are also free to discontinue participating at any time and this will not affect the services you normally get at the public health facilities.

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR HIV TESTING OF SUBJECTS IN SOUTH AFRICA COHORT 2

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 5 (South Africa-specific version) **Date:** 10/07/2006

Company Name: GlaxoSmithKline Biologicals

Subject Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

According to the national guidelines in South Africa, HIV (human immunodeficiency virus) testing of all infants participating in this research study of the HRV vaccine should be ideally performed.

Testing for HIV will be offered and ideally performed for all children in the study at Visit 1. If not performed at Visit 1, testing for HIV will be offered at Visit 4.

Should you agree to the test, you will be given pre-test counselling and you will be asked to study and sign this consent form. After you have signed this consent form (i.e. given written approval that you agree to the HIV test for your baby), a blood sample (± 3 ml which is a bit more than half teaspoon) will be taken from your child/ward to perform the HIV test. You will be informed of the test results at the following visit and post-test counselling will be offered. If necessary, a blood sample (± 2 ml which is a bit less than half teaspoon) will be taken from your child/ward for a confirmatory HIV test at the following visit. Depending on when the HIV test is done and whether a confirmatory HIV test is done, your child/ward will have an additional visit (Visit 5 at 21-48 days after Visit 4) to communicate results of the initial HIV test to you and perform a confirmatory HIV test if required. A contact will be planned in 2 weeks after Visit 5 to inform you about the confirmatory HIV test result and offer further counselling.

You have the choice to refuse the test. If you refuse the test, your child/ward will still continue to participate in the study.

During the entire study period (from Visit 1 up until Visit 6), if your child/ward develops symptoms indicative of AIDS (WHO interim stages III or IV), or has to be hospitalised

with any SAE and HIV testing has not yet been performed, HIV testing will be proposed at the site or, in the case of hospitalisation, at hospital admission if possible.

If your child/ward is tested and found to be HIV positive, the study staff will, where clinically indicated and/or in case of hospitalisation, facilitate access to a HIV staging facility and/or ARV treatment centers during the study. Decisions towards treatment will be taken by appropriate staff at the treatment centres where national guidelines on treatment of HIV positive children are followed. Pre-test and post-test counselling will be offered to all parents or guardians of study subjects who consented to the HIV testing.

Cotrimoxazole prophylaxis will be prescribed for all infants who are HIV exposed according to the South African National Department of Health Guidelines for the Management of HIV-infected Children 2005. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or Prevention of Mother To Child Transmission (PMTCT) programme and is not breast fed by an HIV positive mother, cotrimoxazole prophylaxis will be stopped. If your child/ward is found to be HIV negative after testing at either Visit 1 or Visit 4 or hospitalisation or PTCT programme but is still breastfed by an HIV positive mother, cotrimoxazole prophylaxis will be continued until such time as breast feeding has been discontinued and HIV in the child has been excluded 6 weeks later. If your child/ward is found to be HIV positive, cotrimoxazole prophylaxis will be continued until such time as this prophylaxis has been taken over by the ARV treatment centres to which he/she has been referred. If your child/ward is HIV negative and still HIV exposed (due to breast feeding), he/she will be referred to the local paediatric out-patients department after study end for further HIV testing/continued cotrimoxazole prophylaxis as needed.

CONFIDENTIAL Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification 102248 (rota-037)

Consent statement

The aims and procedures of the HIV testing have been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Informed Consent for HIV testing (South Africa-specific version 5), dated 10/07/2006, 5 pages].

I, ,the parent / legal guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child/ward (subject)

hereby freely give my consent for my child/ward to undergo HIV testing.

I confirm that I have had the opportunity to ask questions about this HIV testing and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child/ward to take part in this HIV testing.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any questions related to my child's/ward's HIV testing during the study.

CONFIDENTIAL

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification 102248 (rota-037)

Consent statement

***Signature (or thumb-print) of Parent / Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

***Printed name of Parent / Legal Guardian** _____

If the parent/legal guardian is illiterate, an Independent Literate Witness should also sign the consent form

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

CONFIDENTIAL Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification 102248 (rota-037)

Statement by Doctor or designated person who conducted the informed consent discussion:

I have carefully explained the aims and procedures of the HIV testing to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

CONFIDENTIAL

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR SECOND YEAR FOLLOW-UP OF SUBJECTS

Study Identification: 102248 (Rota-037), 111274 (ROTA-037 EXT:Y2)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 2 South Africa-specific version **Date:** 30/08/2007

Company Name: GlaxoSmithKline Biologicals

Subject Identification:

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Dear Parent or Guardian:

Your child/ward is part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals. Your child/ward has received three doses of the rotavirus vaccine or its placebo by mouth, 1 month apart.

GSK Biologicals' rotavirus vaccine (Rotarix™) is registered in South Africa and is available in the private market.

Your child/ward was planned to be followed until 12 months of age. We would like to continue the follow-up of your child/ward until the end of the 2008 rotavirus season which will be on 15 September at the latest, as the study period has been extended. This means that your child's/ward's participation in the study will be up to the time that he/she is approximately 18 to 24 months. This would allow us to find out if the vaccine continues to protect young children against severe diarrhoea caused by the rotavirus during the second year of life. Also, there will be a follow-up of your child/ward for adverse events and serious adverse events (i.e. any signs or symptoms which your child/ward manifests and that you perceive as serious) during this extended study period. Your decision to let your child/ward participate in the follow-up period is voluntary.

Your child/ward will have a study visit when he/she is approximately 18 to 24 months of age (Visit 7). The intended duration of the study for your child/ward will not exceed a time period of 24 months (which is an additional time period of approximately 8 to 12 months).

No additional blood samples will be taken from your child/ward during the second year follow-up period to evaluate the rotavirus vaccine. Blood samples may be taken for any HIV testing if needed according to the national guidelines in South Africa.

CONFIDENTIAL

During the second year follow-up, you will continue with the same procedures as during the first year. The study nurse will review all the study procedures with you in detail. The study procedures at Visit 6 (when your child is one year of age) and Visit 7 (when your child is approximately 18 to 24 months of age) are summarised below:

At Visit 6,

- A 'GE diary card' will be provided to you and should be used to record information during each GE episode experienced by your child/ward after Visit 6 until Visit 7 on an ongoing basis as GE episodes occur. The study staff member will help you to complete the diary card during the weekly visits. You should return the completed diary cards on an ongoing basis to the member of the study staff who will visit you weekly.
- You should collect stool samples from your child/ward during each GE episode and return the stool samples to the investigator on an ongoing basis. Also two occurrences of GE should be classified as separate episodes if there are 5 or more GE-free days between the episodes.
- During the study, a member of the study staff will visit you weekly to check if your child/ward had any diarrhoea and to assist/advise you with any other problems your child/ward may have.
- You should contact the study physician or study staff if your child/ward experiences any signs or symptoms that you perceive as serious or if your child/ward is hospitalised during this period.

You should attend the local hospital, or the nearest 24 hour health facility for after-hours consultation.

If your child/ward develops symptoms during the study period, indicative of AIDS (a disease of the immune system) (WHO interim stages III or IV), or has to be hospitalised with any serious adverse event and HIV testing has not yet been performed, HIV testing will be proposed to you at the 24 hour health facility, or in the case of hospitalisation, at hospital admission if possible. HIV testing between Visit 6 - Visit 7 will be proposed only at local clinics or hospitals as indicated as per clinical symptoms. The results of any HIV tests performed during the serious adverse event will be recorded in the SAE report form. All the relevant information regarding your child/ward will be kept confidential.

At Visit 7,

- Visit 7 will be the final visit.
- Your child/ward will be examined by the study doctor.
- You will be asked by the investigator if your child/ward has been sick or hospitalised since the previous visit.
- You will return the completed diary cards to the study staff.
- Study conclusion.

To help with the time and travel expenses, you will be reimbursed R150.00 for the scheduled study visit at the end of the study completed by your child/ward. There will be no charge for study-related doctor visits, examinations, and laboratory tests. If your child/ward is referred to a HIV staging facility and/or ARV treatment centers during the study, transport will be offered through the study project or you will be given R40.00 to cover public transport costs to and from the ARV treatment site.

If you want to stop your child/ward's participation in the study at any stage, please notify your study doctor or site staff.

The names of people who can be contacted for information on the trial and/or medical care

The physician you can contact if you require any additional information or have any questions concerning the trial, availability of medical care or if you think you have experienced a research-related illness or injury.

You may ask questions about the study. If you have any questions, please contact:

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Fax number of investigator:

CONFIDENTIAL Subject ID _____

Study Identification 102248 (Rota-037), 111274 (ROTA-037 EXT:Y2)
Supplementary Written Informed Consent Form for 2nd year follow-up

Consent statement

The procedures of the second year follow-up and HIV testing have been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Written Informed Consent for 2nd year follow-up (Version 2 South Africa-specific version), dated 30/08/2007, 6 pages].

I, ,the parent / legal guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child/ward (subject)

hereby freely give my consent for my child/ward to participate in the 2nd year follow-up.

I confirm that I have had the opportunity to ask questions about the 2nd year follow-up and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child/ward to take part in the 2nd year follow-up.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any questions related to my child's/ward's participation in the 2nd year follow-up during the study.

I have the names of person(s) who I can contact in case of any study-related questions during the study, or if I want to withdraw my child/ward from the study.

Tick as appropriate

I give permission that the samples from my child are stored for up to 15 years for the purpose of further testing for the disease and vaccine under study or for the quality assurance of laboratory tests, excluding genetic research.

I do not give permission that the samples from my child/ward are stored for up to 15 years.

CONFIDENTIAL

Subject ID _____

Study Identification 102248 (Rota-037), 111274 (ROTA-037 EXT:Y2)
Supplementary Written Informed Consent Form for 2nd year follow-up

Consent statement

***Signature of Parent / Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

***Printed name of Parent / Legal Guardian** _____

If the parent/legal guardian is illiterate, an Independent Literate Witness should also sign the consent form

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

CONFIDENTIAL Subject ID _____

Study Identification 102248 (Rota-037), 111274 (ROTA-037 EXT:Y2)
Supplementary Written Informed Consent Form for 2nd year follow-up

Statement by Doctor or designated person who conducted the informed consent discussion:

I have carefully explained the aims and procedures regarding the 2nd year follow-up to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR USING RESULTS OF HIV TESTING AFTER BREAST FEEDING CESSATION

Study Identification: 102248 (Rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 1 South Africa-specific version **Date:** 02/08/2007

Company Name: GlaxoSmithKline Biologicals

Subject Identification:

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Dear Parent or Guardian:

Your child is part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals. Your child/ward has received the rotavirus vaccine or its placebo three times by mouth.

National Department of Health Guidelines for the Management of HIV infected children in South Africa recommends HIV testing 6 weeks after breast feeding cessation. We would like to obtain your consent to allow that the results of this test when performed can be recorded in the "case report form" that is used to record all data collected from your child/ward. All the relevant data pertaining to your child/ward will be kept confidential.

If you have any questions, please contact the site staff the details mentioned below:

Name of study staff:

Address of study staff:

Telephone number of study staff:

Fax number of study staff:

Consent statement

The supplementary written informed consent for recording my child's/ward's results on the HIV testing performed after breast feeding cessation in his/her case report form has been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Written Informed Consent for recording results on the HIV testing performed after breast feeding cessation in his/her case report form (Version 1 South Africa-specific version), dated 02/08/2007, 4 pages].

I, ,the parent / legal guardian of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child/ward (subject)

hereby freely give my consent for recording my child/ward's results on the HIV testing performed after breast feeding cessation in his/her case report form.

I confirm that I have had the opportunity to ask questions on this and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow recording my child/ward's results on the HIV testing performed after breast feeding cessation in his/her case report form.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case I have any questions on this.

Consent statement

***Signature of Parent / Legal Guardian** _____ **Date:** _____

DD/ MM/ YY

***Printed name of Parent / Legal Guardian** _____

If the parent/legal guardian is illiterate, an Independent Literate Witness should also sign the consent form

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Statement by Doctor or designated person who conducted the informed consent discussion:

I have carefully explained the aims and procedures of the HIV testing to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of the Investigator* _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator* _____

* Only required if the Investigator was not the person who was conducting the Consent.

CONFIDENTIAL

WRITTEN INFORMED CONSENT FORM

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**

Simplified Study Title: A study to find out if 2 doses of the HRV vaccine are as good as 3 doses in their ability to protect against diarrhoea caused by rotavirus, and to determine if they are safe when this vaccine is given with routine childhood vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**

Version Number: [redacted] Version 5 **Date:**03/Nov/2005

Company Name: GlaxoSmithKline Biologicals S.A.

Investigator:

DATE AND TIME OF FIRST INFORMED CONSENT DISCUSSION:

Dd	mmm	yyyy

:
Time

Participants Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Written Informed Consent Form
Study Identification 102248 (rota-037)

CONFIDENTIAL

INTRODUCTION

Good day, my name is [redacted] I am a doctor at [redacted] I would like to invite you and your child/ward to consider participating in a clinical trial entitled Rota 037 as described in the following pages.

1. Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time.

2. This information leaflet is to help you to decide if you would like your child/ward to participate. You should fully understand what is involved before you agree to take part in this study.

3. This consent form may contain words that you do not understand. If you have any questions about the study, do not hesitate to ask me or the study doctor or staff to explain anything unfamiliar.

4. In order to help you in understanding this study; you will receive a 2-page summary of this consent form.

5. You will be asked to complete an Informed Consent Feedback Form. Your answers to the questions in this form will allow the person taking informed consent to understand if there are any points that you did not understand. In that case, the informed consent will be again explained to you.

6. You should not agree to take part unless you are satisfied about all the procedures involved.

7. You may not participate in another investigational medicine research study, nor take any other investigational medicine during your participation in this study.

8. You should not have participated in an investigational medicine research study within the past 30 days.

9. Please be completely truthful with me regarding your health history, since you may otherwise harm yourself by participating in this study.

10. Once you understand the study and if you decide that your child/ward may take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

11. If you have a personal doctor, please discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard.

12. The study doctor and/or the institution are paid to conduct this research study by two international organisations: the World Health Organisation (WHO) and the Rotavirus Vaccine Program LLC (RVP). GlaxoSmithKline Biologicals (GSK) is responsible for administration of the study including clinical trial supply management, clinical data collection, analysis and biological samples analysis.

The main objective of this document, called a consent form, is to provide you as the parents or guardians of a child with information necessary to help you make the decision

about whether or not to have your child in this study. The document provides information about the vaccine including the likely advantages and disadvantages associated with the vaccine, the study purpose and the study procedures. This document also tells you about your rights and responsibilities on behalf of your child/ward if you decide to enrol him/her in the study as a participant.

Rotavirus disease

Rotavirus is a leading cause of severe diarrhoea among children. GSK Biologicals, a drug company that tests new vaccines and drugs has developed a new vaccine- the human rotavirus vaccine (referred to as HRV vaccine), for protection of children from developing this type of diarrhoea. The purpose of this research is to find out if 2 doses of this new vaccine are as good as 3 doses, both in terms of providing protection and in being safe. The vaccine that is being tested has to be taken by mouth, (like the polio drops). We wish to invite your child to take part in this research study.

Purpose/Description/Procedures/Duration

The main objective of this document, called a consent form, is to provide you as the parents or guardians of a child with information necessary to help you make the decision about whether or not to have your child in this study. The document provides information about the vaccine including the likely advantages and disadvantages associated with the vaccine, the study purpose and the study procedures. This document also tells you about your rights and responsibilities on behalf of your child/ward if you decide to enrol him/her in the study as a participant

This consent form may contain words that you do not understand. Please ask the study doctor or staff to explain anything unfamiliar, and to answer any questions that you have about the study.

Once you understand the study, you will be asked if you want your child/ward to be in the study. If you do, you will be asked to sign this form.

The study doctor and/or the institution are paid to conduct this research study by two international organisations: the World Health Organisation (WHO) and the Rotavirus Vaccine Program LLC (RVP). GlaxoSmithKline Biologicals (GSK) was responsible for administration of the study including clinical trial supply management, clinical data collection, analysis and biological samples analysis.

This medical research study will be conducted on ***5670*** infants coming for their routine immunisation visits to the study centers in Africa. All healthy infants between the ages of 5-10 weeks can take part in this study. **(Amendment 1: 24 August 2005)**

All children participating in this study will have five study visits (Visits1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) depending on whether a confirmatory HIV test was done. **(Amendment 1: 24 August 2005)**

The main purpose of this study is to find out how well the HRV vaccine works to prevent severe cases of rotavirus diarrhoea. This will be done by giving some children the HRV vaccine and some children a placebo (product that looks like the real vaccine, but does not contain any active ingredient), and comparing the results. We will take stool samples from each child for testing to find the number of rotavirus diarrhoea cases. This will allow us to assess the effectiveness of the HRV vaccine (ability to prevent rotavirus diarrhoea). We will also look for any serious side effects to evaluate safety of HRV vaccine. We will take a blood sample (± 2 ml which is a bit less than half a teaspoon) from some children at the first visit for baseline values. A blood sample (± ***2*** ml which is a bit ***less*** than half a teaspoon) will be taken from all children at Visit 4 to see how your child's/ward's immune system (part of body that fights infection) reacts to the vaccines. **(Amendment 1: 24 August 2005)**

According to the national guidelines in South Africa, HIV (human immunodeficiency virus) testing of all infants should be ideally performed during the study. You will be asked to sign a separate consent form to allow HIV testing. You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling and then a blood sample (±3 ml which is a bit more than half teaspoon) will be taken from your child/ward at Visit 3 to perform the HIV test. You will be informed of the test results at Visit 4 and post-test counselling will be offered. If necessary, a blood sample (±2 ml which is a bit less than half teaspoon) will be taken from your child/ward at Visit 4 for a confirmatory HIV test. If a confirmatory HIV test is done for your child/ward, you will have to visit the clinic approximately two weeks after Visit 4 so that the study staff can inform you of the HIV test results and offer further counselling. (**Amendment 1: 24 August 2005)**

GSK Biologicals will facilitate access to anti-retroviral (ARV) treatment centers according to National Guidelines for any children who test HIV positive, but decisions towards treatment will be taken by appropriate staff at these treatment centers. Pre-test ***and post-test*** counselling will be offered to all mothers or guardians of study subjects ***who consented to the HIV testing***. **(Amendment 1: 24 August 2005)**

Ethical and Regulatory Approval

This clinical study protocol has been submitted to: 1 [redacted] 2) [redacted] 3 [redacted] South Africa, 4 [redacted] 5) [redacted] 6 [redacted]

[redacted] and 7) [redacted] These committees have granted written approval.

The study has been structured in accordance with the 1996 version of Declaration of Helsinki, which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained should you wish to review it.

Study Participation

The duration of this study is for a maximum period of 10 to 11 months. ***All children participating in this study will have five study visits (Visits1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) depending on whether a confirmatory HIV test was done.***

Procedures:

If you are interested to take part in the research, the research staff will ask you questions about your child's/ward's medical history and the medicines that your child/ward may be taking. Your child/ward will not be able to participate in the study if she or he is taking certain kinds of medicines or has certain specific illnesses.

In this study one third of the children will get 3 doses of vaccine, another third will get 2 doses of vaccine and one dose of placebo (an inactive product that looks like the vaccine but has no effect on the body), and the remaining third will get 3 doses of placebo. Randomisation will be used to assign children to one of the three treatment groups. Randomisation means that the participants are put into a group by chance. It is like flipping a coin. Your child/ward will have a 2 out of 3 chance of receiving the HRV vaccine (either three doses of HRV vaccine or two doses of HRV vaccine and one dose of placebo) and a 1 out of 3 chance of receiving a placebo (looks like vaccine but has no activity). Neither you nor your doctor will know whether your child receives the real vaccine or the inactive liquid. If needed in case of emergencies, however, the doctor will be given this information. We need to give inactive placebo to some children to make sure that the effect we see after our research has not occurred because of chance, but occurred because of the vaccine. This is the way that scientific studies are designed.

If your child is eligible to take part in the trial, he/she will receive three doses given four weeks apart. The study vaccine or placebo will be given by mouth. All study participants will be observed closely for at least 30 minutes following the administration of vaccines to monitor any reaction to the vaccine/placebo. As mentioned before, neither the doctor nor you will know what your child has received, but your child will be followed up very carefully to make sure that he gets medical attention when required

During the study, you should contact the study staff or the immediately should your child/ward manifest any signs or symptoms that you perceive as serious. The study staff will be available for your consultation for the entire study period (24 hours/day).

Your child/ward will receive his/her ***nationally recommended vaccinations*** routine vaccinations recommended in South Africa at the same time of the administration of the study vaccine dose. This study in no way alters the routine immunisation schedule, and it is very important for you to follow the recommendations given by the immunisation nurse. **(Amendment 1: 24 August 2005)**

All children participating in this study will have five study visits (Visits1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) depending on whether a confirmatory HIV test was done. **(Amendment 1: 24 August 2005)**

The study is expected to end when your baby will be one year old. The study procedures are summarised below. The study nurse will review all the study procedures with you in detail.

- At Visits 1, 2 and 3 that will take place four weeks apart, the doctor will examine each child and give a dose of HRV or its placebo by mouth. At each of these visits, you will receive a diary card to collect information on diarrhoea.
- Each child will also receive all the routine vaccines at Visits 1, 2 and 3. For other routine vaccinations (at 9 months of age), you will be requested to take your child/ward to your local clinic.
- Visits 4, 5 *and 6* are follow-up visits. (Amendment 1: 24 August 2005)
  - Visit 4 will take place one month after Visit 3.
  - ***Visit 5 will only take place if your child/ward had a confirmatory HIV test at Visit 4. The confirmatory HIV test results will be communicated to you at this visit. There will no other study procedures.*** **(Amendment 1: 24 August 2005)**
  - Visit 6 will be the final visit and will take place when your child/ward is one year old.
- At each visit, the investigator will ask you if your child/ward has suffered any serious adverse event(s) since the previous visit.
- A blood sample (± 2 ml which is a bit less than half a teaspoon) will be collected from the most convenient and safe site from a subset of ***570*** infants at Visit 1. This blood sample will be tested to measure the baseline amount of substance in the blood that fights infection (called antibodies). **(Amendment 1: 24 August 2005)**
- A blood sample (± ***2*** ml which is a bit ***less*** than half a teaspoon) will be collected from the most convenient and safe site from all infants at Visit 4. This blood sample

will be tested to measure the amount of substance in the blood that fights infection (called antibodies). This will allow the researchers to see how your child's/ward's reacts to the vaccines to fight infection (called immune response). **(Amendment 1: 24 August 2005)**

- ***At Visit 3, the study staff will ask whether your child/ward has been exposed to HIV. A separate Informed Consent form will be provided to you at Visit 3 to seek your permission to perform HIV testing for your child/ward. You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling and then a blood sample (±3 ml which is a bit more than half teaspoon) will be taken from your child/ward at Visit 3 to perform the HIV test. You will be informed of the test results at Visit 4 and post-test counselling will be offered. If necessary, a blood sample (±2 ml which is a bit less than half teaspoon) will be taken from your child/ward at Visit 4 for a confirmatory HIV test. If a confirmatory HIV test is done for your child/ward, you will have to visit the clinic for Visit 5 (approximately two weeks after Visit 4) so that the study staff can inform you of the HIV test results and offer further counselling.*** **(Amendment 1: 24 August 2005)**
- ***If your child/ward develops symptoms indicative of AIDS (WHO stages II or III), or has to be hospitalised before Visit 3, HIV testing, counselling and the concerned Informed Consent will be proposed to you before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.*** **(Amendment 1: 24 August 2005)**
- GSK Biologicals will facilitate access to ARV treatment centers for any children who test HIV positive, but decisions towards treatment will be taken by appropriate staff at these treatment centers. Pre-test ***and post-test*** counselling will be offered to all mothers or guardians of study subjects ***who consented to HIV testing***. **(Amendment 1: 24 August 2005)**
- At the first visit, you will receive a Trial Identification Card, which will specify details of the trial, 24-hour telephone number of the study doctor, study nurses and study staff.
- During the study, a member of the study staff will visit you weekly to check if your child/ward had any diarrhoea.
- If you feel that your child/ward has symptoms of severe diarrhoea, you should take him/her to the nearest hospital/medical facility. The hospital/medical facility that is currently nearest to you is: _____. You should show the Trial Identification Card to any health care professional that you consult.

- You should contact the study staff or doctor immediately should your child/ward manifest any signs or symptoms you perceive as serious. The study staff will be available at all times.
- When your child/ward has diarrhoea, you will be asked to complete a Diary Card daily until end of diarrhoea. The information requested on the Diary Cards includes taking your child's/ward's temperature and noting information on the diarrhoea episode. The study staff member will help you to complete the diary card during the weekly visits.
- You will be asked to take stool samples from your child/ward if he/she develops diarrhoea at any time from Visit 1 to Visit ***6***. Containers for collection of stool samples will be provided to you. You should contact the study staff to pick up the sample once it has been collected. **(Amendment 1: 24 August 2005)**
- If you agree, the blood sample(s) may be stored for a long time (up to 15 years). You will be asked to complete the consent form, on page 15 of this document, to state your decision.

Your responsibilities are:

- to follow the instructions given by the study doctor and the study staff,
- to bring your child to the clinic at scheduled visits and to answer the final questions at the end of the study,
- to complete the information requested on the Diary Cards which includes taking your child's/ward's temperature and noting information on the diarrhoea episode,
- to promptly report to the study staff any unexpected or serious events your child/ward may experience.

If you want to stop your child's/ward's participation in the study or if you find you have not followed instructions listed above, it is important that you notify the study doctor or study staff.

Number of Participants

This study will involve a total of approximately ***5670*** infants at several sites in Africa. ***A minimum of 2,600 subjects and up to a maximum of 3,000 subjects are planned to be enrolled in South Africa.*** **(Amendment 1: 24 August 2005)**

Recruitment of new participants in this study will stop when the planned number of participants has been achieved.

The names of people who can be contacted for information on the trial and/or medical care

For the duration of the study, you will be under the care of Dr [redacted] and Dr [redacted] If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact me.

Other doctors from this department who are working on this study are:

List contact details and designation (Principal Investigator/Co- or Sub-Investigator) of the study doctors

The 24-hour telephone number through which you can reach me or another authorised person, i [redacted](Dr [redacted] or [redacted](Dr [redacted]

The physician you can contact if you require any additional information or have any questions concerning the trial, availability of medical care or if you think you have experienced a research-related illness or injury.

You may ask questions about the study. If you have any questions, please contact:

Name of Investigator: [redacted]

Address of Investigator: [redacted]

Telephone number of investigator: [redacted]

Fax number of investigator: [redacted]

Risks/Inconveniences

Over 80,000 adults, children, and infants have participated in studies with the rotavirus vaccine. During these studies, over 37,000 infants received at least one dose of the vaccine. The rotavirus vaccine caused only mild side effects in some infants that were similar to those observed in infants who were given a placebo (product that looks like the real vaccine, but does not contain any active ingredient). The vaccine will not cause the rotavirus disease.

Seven years ago, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage of the small intestine that requires immediate attention by a doctor. If intussusception is recognised

early, treatment can be given for complete recovery. Because RotaShield™ may have increased the risk of intussusception, it is no longer available. If you are interested, your doctor can give you more information on intussusception.

The rotavirus vaccine used in this study was tested in a large study with 63,225 children and results showed that this rotavirus vaccine being tested in this study does not increase the risk of intussusception.

There may be momentary, mild discomfort and bruising of the skin on the arm 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 or haemoglobin that may be caused due to loss of blood).

Your child/ward will receive routine DTPw-HBV/Hib and OPV vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, or crying.

As with any experimental vaccine, unexpected serious adverse experiences, including allergic reactions to the vaccine, may occur. All the medical equipment to treat any serious reactions to the study vaccine will be available.

You will be informed of any new findings developed during the course of this research study.

Benefits

If the vaccine is efficacious in this population, infants who receive the vaccine may have the benefit of being protected against rotavirus diseases. Infants who receives a placebo will not have this benefit, however if this vaccine proves to be useful, your child's/ward's participation will benefit other children in the future.

If your child/ward is found to be HIV positive and is eligible for treatment, GSK Biologicals will facilitate access to ARV treatment centers.

There will be no charge for study-related doctor visits, examinations and laboratory tests.

Alternative Treatment/Measure of Prevention

There is no licensed rotavirus vaccine currently available in the Republic of South Africa.

Disease caused by rotavirus is treated with oral rehydration solutions or if necessary, intravenous fluid replacement. This is to prevent dehydration and shock. There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Joining this study is voluntary. If you decide against joining, there will be no penalty. You and your child/ward will lose no benefits.

Compensation for Study-Related Injury

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that the sponsor, GlaxoSmithKline without legal commitment, should compensate you without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for the study. GlaxoSmithKline will not compensate you for any procedure carried out which is not in accordance with the protocol for the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. A copy of the guidelines for compensation for a possible injury/disablement that occurs while taking part in this study can be obtained from your doctor.

Payment to Participants

You will receive no payment for your child's/ward's participation in this study.

Expenses/Costs

To help with the time and travel expenses, you will be reimbursed R100 for each scheduled study visit completed by your child/ward. There will be no charge for study-related doctor visits, examinations, and laboratory tests. All study vaccines will be provided free of charge.

If your child/ward is found to be HIV positive and is eligible for ARV treatment, you will be referred to the nearest ARV treatment roll-out site. You will be given up to R40.00 in proportion to the distance and return public transport costs to and from the ARV treatment site.

Right to ask questions and/or withdraw from the study

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact Prof. [redacted] Chairperson of the [redacted] which is an independent committee established to help protect the rights of research participants at [redacted]

For research information you can contact the study doctor who has or can obtain all information on research done with the study vaccine.

If you have any questions about this trial you should first discuss them with your doctor or the ethics committee. After you have contacted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar

SA Medicine Control Council

Department of Health

Private Bag X828 PRETORIA 0001

Personal Doctor / Specialist option

Please indicate below, whether you want me to notify your child's/ward's personal doctor or your child/ward's specialist of their participation in this study:

☐ YES, I want you to inform my child's/ward's personal doctor/specialist of their participation in this study.

☐ NO, I do not want you to inform my child's/ward's personal doctor/specialist of their participation in this study.

☐ My child/ward does not have a personal doctor/specialist.

Termination of Subjects' Study Participation

Your child's/ward's participation in the study may be stopped for any of the following reasons:

- If you do not follow the study doctor's instructions,
- The study doctor decides it is in the best interest of your child's/ward's health and welfare to discontinue participation in the study,
- There are either not enough subjects interested in participating in the study or the study has reached the required number of subjects,
- GSK Biologicals has decided to stop the study at this site for other reasons not known at this time,
- GSK Biologicals stops enrolling new subjects into study for any reason, and your child/ward is in the screening phase of the study and has not yet been assigned to one of the vaccine groups.

Voluntary Participation and Subjects Right to End Participation

Your child's/ward's participation in this study is voluntary. If you do decide for your child/ward to take part, you will be given this information to keep and be asked to sign this consent form. 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. You must inform your study doctor if you decide to do this. 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.

Any information and results collected before your child's/ward's withdrawal from the study will be used by GlaxoSmithKline.

Confidentiality and Data Privacy

Maintaining confidentiality is important to GlaxoSmithKline Biologicals S. A., WHO and RVP. Your child's/ward's personal information (for example, gender, age, the details of his/her medical conditions) and other information (the data collected by GlaxoSmithKline as part of the study) will be identified by a number (i.e., coded). Your child's/ward's name will not appear in any publications or reports produced from this study.

GlaxoSmithKline Biologicals S. A. will keep the information and the results collected about your child/ward in this study. Your child's/ward's name and address are not included in the information kept by GlaxoSmithKline Biologicals S. A. - only your study doctor will keep this information. GlaxoSmithKline Biologicals S. A. has told your study doctor to keep the information about your child/ward in a secure place. GlaxoSmithKline will comply with internal procedures to protect personal and other information even in countries where data privacy laws are less strict than in Europe/US.

By agreeing to take part in this research study you will be allowing certain persons to see the information about your child/ward (both personal, including his/her name, and other information) held by the study doctor. Your child's/ward's information will be looked at to confirm that it is correct and that it is related to your child/ward. This will be done by selected people working for GlaxoSmithKline and organisations acting on behalf of GlaxoSmithKline Biologicals S. A., [redacted] along with the government regulatory authorities. These persons are required to maintain the confidentiality of your information.

Your child's/ward's information will be processed electronically (i.e., by a computer) or manually and analysed to determine outcome of this study. GlaxoSmithKline may use your child's/ward's information for other medical/health care purposes related to development of this vaccine. For this purpose only your child's/ward's coded information will be used.

Your child's/ward's information may be sent to regulatory authorities, to the IEC/IRB, to other doctors and/or organisations working with GlaxoSmithKline. It may also be sent to other GlaxoSmithKline sites in this country and in other countries where there may be different or lesser standards for looking after it. GlaxoSmithKline will apply the same standard in the protection of your information to the extent permitted by law.

You have the right to ask the study doctor about the data being collected on your child/ward for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your child's/ward's personal information and to have any needed corrections to it made.

Notification of New Information

Sometimes during the course of a research project, new information becomes available about the vaccine that is being studied. If this happens, we will tell you about new information that may affect you and your child/ward's willingness to stay in this study.

Consent statement

The HUMAN ROTAVIRUS vaccine study has been clearly explained to me and I have read and understood the information provided [A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants, Version 2, dated 24/08/2005, 16 pages].

I, _____, the legal representative of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child /ward (subject)

hereby freely give my consent for my child/ward to take part in this [clinical/vaccine] study.

I 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.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child /ward to take part in this study.

I agree to take part in this study and to my child / ward's participation in this study. I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any study-related questions during the study, or if I want to withdraw my child from the study.

CONFIDENTIAL

Consent statement

_____
Printed name of child/ward (subject)

***Signature of Legal Representative** _____ **Date:** _____
DD/ MM/ YY

***Printed name of Legal Representative** _____

If the legal representative is illiterate, an Independent Literate Witness should also sign the consent form (if possible, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

Signature of Witness _____ **Date:** _____
DD/ MM/ YY

Printed name of Witness _____

Signature of Person conducting Consent _____ **Date:** _____
DD/ MM/ YY

Printed Name of Person conducting Consent _____

Signature of Investigator* _____ **Date:** _____
DD/ MM/ YY

Printed Name Investigator* _____

***only required if the Investigator was not the person conducting the Consent**

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of Investigator* _____ **Date:**

DD/ MM/ YY

Printed Name Investigator* _____

*only required if the Investigator was not the person conducting the Consent

CONFIDENTIAL

Consent for Storage and Future Use of Leftover Specimens

Collected samples may be stored and used for purposes related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably.

Collected samples may also be anonymised (meaning that the link between your child/ward and the sample will be destroyed) to be used for other research purposes.

Collected samples may be stored for a long time (up to 15 years) and used for purposes related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably. You will be asked to complete the consent form, on page 16 of this document, to state your decision.

CONFIDENTIAL

If any of the specimens my child/ward has provided for this research project are left over after 15 years (Tick **one** choice from each of the following boxes)

- ☐ I wish this leftover material to be destroyed immediately
- ☐ I give permission for this leftover material to be stored and used in future research but only on the same subject as the current research project with the approval of the Ethics Committee.
- ☐ I give permission for this leftover material to be stored and used in future research of any type (**No Genetic Research will be conducted on the stored samples)**

- ☐ I want this leftover material to be destroyed after ____ years.
- ☐ I give permission for this leftover material to be stored indefinitely

- ☐ I want my identity to be removed from the left over specimens.
- ☐ I want my identity to be kept with the left over specimens

Print Name of Subject | Date and Signature of parent/guardian

_____ | _____

___/___/___ *(dd/mm/yy)*

If illiterate:

Print Name of Independent Literate Witness | Date and Signature of Witness

(ideally, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

_____ | _____

___/___/___ *(dd/mm/yy)*

Person conducting Consent / Researcher:

Print Name of Researcher | Date and Signature of Researcher

CONFIDENTIAL

_____ _____

___/___/___ (dd/mm/yy)

Investigator*:

Print Name of Investigator* Date and Signature of Investigator*

_____ _____

___/___/___ (dd/mm/yy)

*only required if the Investigator was not the person conducting the Consent

SUPPLEMENTARY WRITTEN INFORMED CONSENT FORM FOR HIV TESTING OF SUBJECTS

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Simplified Study Title: A study to find out if 2 doses of the HRV vaccine are as good as 3 doses in their ability to protect against diarrhoea caused by rotavirus, and to determine if they are safe when this vaccine is given with routine childhood vaccinations in healthy infants.

Version Number: [redacted] Version 1 **Date:** 04/11/2005

Company Name: GlaxoSmithKline Biologicals S.A.

Investigator:

DATE AND TIME OF FIRST INFORMED CONSENT DISCUSSION:

Dd	mmm	yyyy

:
Time

Participants Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

To the mother/legal guardian of study participant,

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

According to the national guidelines in South Africa, HIV (human immunodeficiency virus) testing of all infants participating in this research study of the HRV vaccine should be ideally performed.

Should you agree to the test, you will be given pre-test counselling and then a blood sample (± 3ml which is a bit more than half teaspoon) will be taken from your child/ward at Visit 3 to perform the HIV test. You will be informed of the test results at Visit 4 and post-test counselling will be offered. If necessary, a blood sample (± 2ml which is a bit less than half teaspoon) will be taken from your child/ward at Visit 4 for a confirmatory HIV test. If a confirmatory HIV test is done for your child/ward, you will have to visit the clinic approximately two weeks after Visit 4 so that the study staff can inform you of the HIV test results and offer further counselling.

You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study.

GSK Biologicals will facilitate access to ARV treatment centers for any children who test HIV positive, but decisions towards treatment will be taken by appropriate staff at these treatment centers. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who give their consent for HIV testing.

Consent statement

The aims and procedures of the HIV testing have been clearly explained to me and I have read the information sheet and understand the information provided [Supplementary Informed Consent for HIV testing, Version 1, dated 24/08/2005, 6 pages].

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

I, , the legal representative of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child /ward (subject)

hereby freely give my consent for my child/ward to undergo HIV testing.

I 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.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child /ward to take part in this study.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any study-related questions during the study, or if I want to withdraw my child from the study.

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

Consent statement

_____
Printed name of child/ward (subject)

***Signature of Legal Representative** _____ **Date:** _____
DD/ MM/ YY

***Printed name of Legal Representative** _____

If the legal representative is illiterate, an Independent Literate Witness should also sign the consent form (if possible, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

Signature of Witness _____ **Date:** _____
DD/ MM/ YY

Printed name of Witness _____

Signature of Person conducting Consent _____ **Date:** _____
DD/ MM/ YY

Printed Name of Person conducting Consent _____

Signature of Investigator* _____ **Date:** _____
DD/ MM/ YY

Printed Name Investigator* _____ _____

*only required if the Investigator was not the person conducting the Consent

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of Investigator* _____ Date:

DD/ MM/ YY

Printed Name Investigator* _____

***only required if the Investigator was not the person conducting the Consent**

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

Consent for Storage and Future Use of Leftover Specimens

Collected samples may be stored and used for purposes related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably.

Collected samples may also be anonymised (meaning that the link between your child/ward and the sample will be destroyed) to be used for other research purposes.

Collected samples may be stored for a long time (up to 15 years) and used for purposes related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably. You will be asked to complete the consent form, on page 8 of this document, to state your decision.

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

If any of the specimens my child/ward has provided for this research project are left over after 15 years (Tick **one** choice from each of the following boxes)

- ☐ I wish this leftover material to be destroyed immediately
- ☐ I give permission for this leftover material to be stored and used in future research but only on the same subject as the current research project with the approval of the Ethics Committee.
- ☐ I give permission for this leftover material to be stored and used in future research of any type (**No Genetic Research will be conducted on the stored samples)**

- ☐ I want this leftover material to be destroyed after ____ years.
- ☐ I give permission for this leftover material to be stored indefinitely

- ☐ I want my identity to be removed from the left over specimens.
- ☐ I want my identity to be kept with the left over specimens

Print Name of Subject | Date and Signature of parent/guardian

_____ | _____

___/___/___ *(dd/mm/yy)*

If illiterate:

Print Name of Independent Literate Witness | Date and Signature of Witness

(ideally, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

_____ | _____

___/___/___ *(dd/mm/yy)*

Print Name of Researcher | Date and Signature of Researcher

_____ | _____

English SupplementaryInformed Consent for HIV testing
Version 1: 24 Aug 2005
[redacted] Version 1: 04 Nov 2005
Investigator's Name [redacted]
Approved by [redacted]
Date of approval: 29 Nov 2005

Participant's Initials: __ __ __

Participant Number: _____

Subject ID _____

Supplementary Written Informed Consent Form for HIV Testing of Subjects
Study Identification rota-037

CONFIDENTIAL

___/___/___ *(dd/mm/yy)*

Person conducting Consent / Researcher:

Print Name of Researcher

_____

Date and Signature of Researcher

_____

___/___/___ (dd/mm/yy)

Investigator*:

Print Name of Investigator*

_____

Date and Signature of Investigator*

_____

___/___/___ (dd/mm/yy)

*only required if the Investigator was not the person conducting the Consent

WRITTEN INFORMED CONSENT FORM

Study Identification: 102248 (rota-037)

Study Title: : A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**

Simplified Study Title: A study to find out if 2 doses of the HRV vaccine are as good as 3 doses in their ability to protect against diarrhoea caused by rotavirus, and to determine if they are safe when this vaccine is given with routine childhood vaccinations in healthy infants. **(Amendment 1: 24 August 2005)**

Version Number: [redacted] **Version 4** **Date: 04/11/2005**

Company Name: GlaxoSmithKline Biologicals S.A.

Subject Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

Purpose/Description/Procedures/Duration

Rotavirus is a leading cause of severe diarrhoea among children. GSK Biologicals, a drug company that tests new vaccines and drugs has developed a new vaccine- the human rotavirus vaccine (referred to as HRV vaccine), for protection of children from developing this type of diarrhoea. The purpose of this research is to find out if 2 doses of this new vaccine are as good as 3 doses, both in terms of providing protection and in being safe. The vaccine that is being tested has to be taken by mouth, (like the polio drops). We wish to invite your child to take part in this research study.

The main objective of this document, called a consent form, is to provide you as the parents or guardians of a child with information necessary to help you make the decision about whether or not to have your child in this study. The document provides information about the vaccine including the likely advantages and disadvantages associated with the vaccine, the study purpose and the study procedures. This document also tells you about your rights and responsibilities on behalf of your child/ward if you decide to enrol him/her in the study as a participant

Written Informed Consent Form
Study Identification 102248 (rota-037)

CONFIDENTIAL

This consent form may contain words that you do not understand. Please ask the study doctor or staff to explain anything unfamiliar, and to answer any questions that you have about the study.

In order to help you in understanding this study; you will receive a 2-page summary of this consent form.

You will be asked to complete an Informed Consent Feedback Form. Your answers to the questions in this form will allow the person taking informed consent to understand if there are any points that you did not understand. In that case, the informed consent will be again explained to you.

Once you understand the study, you will be asked if you want your child/ward to be in the study. If you do, you will be asked to sign this form.

The study doctor and/or the institution are paid to conduct this research study by one international organisation: Program for Appropriate Technology in Health (PATH). GlaxoSmithKline Biologicals (GSK) is responsible for administration of the study including clinical trial supply management, clinical data collection, biological samples analysis and analysis of results.

This medical research study will be conducted on 5670 infants coming for their routine immunisation visits to the study centres in South Africa. All healthy infants between the ages of 5-10 weeks can take part in this study.(Amendment 1:24 August 2005).

***All children participating in this study will have five study visits (Visits1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) depending on whether a confirmatory HIV test was done.* (Amendment 1: 24 August 2005)**

The main purpose of this study is to find out how well the HRV vaccine works to prevent severe cases of rotavirus diarrhoea. This will be done by giving some children the HRV vaccine and some children a placebo (product that looks like the real vaccine, but does not contain any active ingredient), and comparing the results. We will take stool samples from each child that has a diarrhoeal episode for testing to find the number of rotavirus diarrhoea cases. This will allow us to assess the effectiveness of the HRV vaccine (ability to prevent rotavirus diarrhoea). We will also look for any serious side effects to evaluate safety of HRV vaccine. We will take a blood sample (± 2 ml which is a bit less than half a teaspoon) from some children at the first visit for baseline values. A blood sample (± 2 ml which is a bit more than half a teaspoon) will be taken from all children at Visit 4 to see how your child's/ward's immune system (part of body that fights infection) reacts to the vaccines and to perform HIV testing. The reason for wanting to test your child for HIV is to allow us to find out if the vaccine works and is safe in HIV infected as well as in HIV uninfected children. We will provide you with more details about the HIV testing when we do the test on your child. (Amendment 1:24 August 2005)

According to the national guidelines in South Africa, HIV (human immunodeficiency virus) testing of all infants should be ideally performed during the study. You will be asked to sign a separate consent form to allow HIV testing. You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the

***study. Should you agree to the test, you will be given pre-test counselling and then a blood sample (±3 ml which is a bit more than half teaspoon) will be taken from your child/ward at Visit 3 to perform the HIV test. You will be informed of the test results at Visit 4 and post-test counselling will be offered. If necessary, a blood sample (±2 ml which is a bit less than half teaspoon) will be taken from your child/ward at Visit 4 for a confirmatory HIV test. If a confirmatory HIV test is done for your child/ward, you will have to visit the clinic approximately two weeks after Visit 4 so that the study staff can inform you of the HIV test results and offer further counselling. (*Amendment 1: 24 August 2005)**

GSK Biologicals will facilitate access to anti-retroviral (ART) treatment centres according to National Guidelines for any children who test HIV positive at Visit 4, but decisions towards treatment will be taken by appropriate staff at these treatment centres. Pre-test and post-test counselling will be offered to all mothers or guardians of study subjects who consented to the HIV testing **(Amendment 1: 24 August 2005)**..

Ethical and Regulatory Approval

This clinical study protocol has been submitted and written approval has been obtained from the following:

1) [redacted]
South Africa.

2) [redacted] South Africa

3) [redacted] South Africa.

4) [redacted]
South Africa.

5) [redacted] Switzerland

Note: Program for Appropriate Technology in Health (PATH), [redacted] has deferred approval to the [redacted]

The study has been structured in accordance with the 1996 version of Declaration of Helsinki, which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained should you wish to review it.

Study Participation

The duration of this study is for a maximum period of 10 to 11 months. ***All children participating in this study will have five study visits (Visits1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) depending on whether a confirmatory HIV test was done.***

If you are interested to take part in the research, the research staff will ask you questions about your child's/ward's medical history and the medicines that your child/ward may be taking. Your child/ward will not be able to participate in the study if she or he is taking certain kinds of medicines or has certain specific illnesses.

In this study one third of the children will get 3 doses of vaccine, another third will get 2 doses of vaccine and one dose of placebo (an inactive product that looks like the vaccine but has no effect on the body), and the remaining third will get 3 doses of placebo. Randomisation will be used to assign children to one of the three treatment groups. Randomisation means that the participants are put into a group by chance. It is like flipping a coin. Your child/ward will have a 2 out of 3 chance of receiving the HRV vaccine (either three doses of HRV vaccine or two doses of HRV vaccine and one dose of placebo) and a 1 out of 3 chance of receiving a placebo (looks like vaccine but has no activity). Neither you nor your doctor will know whether your child receives the real vaccine or the inactive liquid. If needed in case of emergencies, however, the doctor will be given this information. We need to give inactive placebo to some children to make sure that the effect we see after our research has not occurred because of chance, but occurred because of the vaccine. This is the way that scientific studies are designed.

If your child is eligible to take part in the trial, he/she will receive three doses given four weeks apart. The study vaccine or placebo will be given by mouth. All study participants will be observed closely for at least 30 minutes following the administration of vaccines to monitor any reaction to the vaccine/placebo. As mentioned before, neither the doctor nor you will know what your child has received, but your child will be followed up very carefully to make sure that he gets medical attention when required

During the study, you should contact the study staff or the immediately should your child/ward manifest any signs or symptoms that you perceive as serious. The study staff will be available for your consultation for the entire study period (24 hours/day).

Your child/ward will receive his/her ***nationally recommended vaccinations*** in South Africa at the same time of the administration of the study vaccine dose. This study in no way alters the routine immunisation schedule, and it is very important for you to follow the recommendations given by the immunisation nurse. **(Amendment 1: 24 August 2005)**

All children participating in this study will have five study visits (Visits1, 2, 3, 4 and 6). The study staff will inform you if your child/ward may have one additional visit (Visit 5) depending on whether a confirmatory HIV test was done. **(Amendment 1: 24 August 2005)**

The study is expected to end when your baby will be one year old. The study procedures are summarised below. The study nurse will review all the study procedures with you in detail.

- At Visits 1, 2 and 3 that will take place four weeks apart, the doctor will examine each child and give a dose of HRV or its placebo by mouth. At each of these visits, you will receive a diary card to collect information on diarrhoea.
- Each child will also receive all the routine vaccines at Visits 1, 2 and 3. For other routine vaccinations (at 9 months of age), you will be requested to take your child/ward to your local clinic.
- Visits 4 ,5 and 6 are follow-up visits. (Amendment 1: 24 August 2005)

- Visit 4 will take place one month after Visit 3.
- ***Visit 5 will only take place if your child/ward had a confirmatory HIV test at Visit 4. The confirmatory HIV test results will be communicated to you at this visit. There will no other study procedures.* (Amendment 1: 24 August 2005).**
- ***Visit 6 will be the final visit and will take place when your child/ ward is one year old.***
- At each visit, the investigator will ask you if your child/ward has suffered any serious adverse event(s) since the previous visit.
- A blood sample (± 2 ml which is a bit less than half a teaspoon) will be collected from the most convenient and safe site from a subset of 570 infants at Visit 1. This blood sample will be tested to measure the baseline amount of substance in the blood that fights infection (called antibodies). (Amendment 1: 24 August 2005)
- A blood sample (± 2 ml which is a bit less than half a teaspoon) will be collected from the most convenient and safe site from all infants at Visit 4. This blood sample will be tested to measure the amount of substance in the blood that fights infection (called antibodies). This will allow the researchers to see how your child's/ward's reacts to the vaccines to fight infection (called immune response). (Amendment 1: 24 August 2005)
- ***At Visit 3, the study staff will ask whether your child/ward has been exposed to HIV. A separate Informed Consent form will be provided to you at Visit 3 to seek your permission to perform HIV testing for your child/ward. You have the choice to refuse the test. If you refuse the test, your child will still continue to participate in the study. Should you agree to the test, you will be given pre-test counselling and then a blood sample (±3 ml which is a bit more than half teaspoon) will be taken from your child/ward at Visit 3 to perform the HIV test. You will be informed of the test results at Visit 4 and post-test counselling will be offered. If necessary, a blood sample (±2 ml which is a bit less than half teaspoon) will be taken from your child/ward at Visit 4 for a confirmatory HIV test. If a confirmatory HIV test is done for your child/ward, you will have to visit the clinic for Visit 5 (approximately two weeks after Visit 4) so that the study staff can inform you of the HIV test results and offer further counselling.* (Amendment 1: 24 August 2005)**
- ***If your child/ward develops symptoms indicative of AIDS (WHO stages II or III), or has to be hospitalised before Visit 3, HIV testing, counselling and the concerned Informed Consent will be proposed to you before Visit 3. In case of HIV testing and positive result before Visit 3, the test will not be repeated at Visit 3. A confirmatory HIV test will be performed as necessary.* (Amendment 1: 24 August 2005)**
- GSK Biologicals will facilitate access to ART treatment centres for any children who test HIV positive at Visit 4, but decisions towards treatment will be taken by appropriate staff at these treatment centres. Pre-test and post-test counselling will be offered to mothers or guardians

of HIV positive subjects at the centres who consented to HIV testing (Amendment 1: 24 August 2005) .

- At the first visit, you will receive a Trial Identification Card, which will specify details of the trial, 24-hour telephone number of the study doctor, study nurses and study staff.
- During the study, a member of the study staff will visit you weekly to check if your child/ward had any diarrhoea.
- If you feel that your child/ward has symptoms of severe diarrhoea, you should take him/her to the nearest hospital/medical facility. The hospital/medical facility that is currently nearest to you is: _____. You should show the Trial Identification Card to any health care professional that you consult.
- You should contact the study staff or doctor immediately should your child/ward manifest any signs or symptoms you perceive as serious. The study staff will be available at all times.
- When your child/ward has diarrhoea, you will be asked to complete a Diary Card daily until end of diarrhoea. The information requested on the Diary Cards includes taking your child's/ward's temperature and noting information on the diarrhoea episode. The study staff member will help you to complete the diary card during the weekly visits.
- You will be asked to take stool samples from your child/ward if he/she develops diarrhoea at any time from Visit 1 to Visit 6. Containers for collection of stool samples will be provided to you. You should contact the study staff to pick up the sample once it has been collected. (Amendment 1:24 August 2005)
- If you agree, the blood sample(s) may be stored for a long time (up to 15 years). You will be asked to complete the consent form, on page 15 of this document, to state your decision.

Your responsibilities are:

- to follow the instructions given by the study doctor and the study staff,
- to bring your child to the clinic at scheduled visits and to answer the final questions at the end of the study,
- to complete the information requested on the Diary Cards which includes taking your child's/ward's temperature and noting information on the diarrhoea episode,
- to promptly report to the study staff any unexpected or serious events your child/ward may experience.

If you want to stop your child's/ward's participation in the study or if you find you have not followed instructions listed above, it is important that you notify the study doctor or study staff.

Number of Subjects

This study will involve a total of approximately 5670 infants at several sites in Africa. ***A minimum of 2,600 subjects and up to a maximum of 3,000 subjects are planned to be enrolled in South Africa.*** **(Amendment 1: 24 August 2005)**

Recruitment of new participants in this study will stop when the planned number of participants has been achieved.

The names of people who can be contacted for information on the trial and/or medical care

The physician you can contact if you require any additional information or have any questions concerning the trial, availability of medical care or if you think you have experienced a research-related illness or injury.

You may ask questions about the study. If you have any questions, please contact:

Name of Investigator:

Address of Investigator:

Telephone number of investigator:

Fax number of investigator:

Risks/Inconveniences

Over 80,000 adults, children, and infants have participated in studies with the rotavirus vaccine. During these studies, over 37,000 infants received at least one dose of the vaccine. The rotavirus vaccine caused only mild side effects in some infants that were similar to those observed in infants who were given a placebo (product that looks like the real vaccine, but does not contain any active ingredient). The vaccine will not cause the rotavirus disease.

Seven years ago, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage of the small intestine that requires immediate attention by a doctor. If intussusception is recognised early, treatment can be given for complete recovery. Because RotaShield™ may have increased the risk of intussusception, it is no longer available. If you are interested, your doctor can give you more information on intussusception.

The rotavirus vaccine used in this study was tested in a large study with 63,225 children and results showed that this rotavirus vaccine being tested in this study does not increase the risk of intussusception.

There may be momentary, mild discomfort and bruising of the skin on the arm 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 or haemoglobin that may be caused due to loss of blood).

Your child/ward will receive routine DTPw-HBV/Hib and OPV vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, or crying.

As with any experimental vaccine, unexpected serious adverse experiences, including allergic reactions to the vaccine, may occur. All the medical equipment to treat any serious reactions to the study vaccine will be available.

You will be informed of any new findings developed during the course of this research study.

Benefits

If the vaccine is efficacious in this population, infants who receive the vaccine may have the benefit of being protected against rotavirus diseases, however this cannot be guaranteed. Infants who receive a placebo will not have this benefit, however if this vaccine proves to be useful, your child's/ward's participation will benefit other children in the future.

If your child/ward is found to be HIV positive and is eligible for treatment, GSK Biologicals will facilitate access to ART treatment centres.

There will be no charge for study-related doctor visits, examinations and laboratory tests.

Alternative Treatment/Measure of Prevention

There is no licensed rotavirus vaccine currently available in the Republic of South Africa.

Disease caused by rotavirus is treated with oral re-hydration solutions or if necessary, intravenous fluid replacement. This is to prevent dehydration and shock. There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Joining this study is voluntary. If you decide against joining, there will be no penalty. You and your child/ward will lose no benefits.

Compensation and or treatment for Study-Related Injury

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Broadly speaking the ABPI guidelines recommend that the sponsor, GlaxoSmithKline without legal commitment, should compensate you and you will receive medical treatment for a trial related injury without you having to prove that it is at fault. This applies in cases where it is likely that such injury results from giving any new drug or any other procedure carried out in accordance with the protocol for the study. GlaxoSmithKline will not compensate you for any procedure carried out which is not in accordance with the protocol for the study. Your right at law to claim compensation for injury where you can prove negligence is not affected. A copy of the guidelines for compensation for a possible injury/disablement that occurs while taking part in this study can be obtained from your doctor.

Payment to Subjects

You will receive no payment for your child's/ward's participation in this study.

Expenses/Costs

To help with the out-of-pocket expenses only, you will be reimbursed R150.00 for each scheduled study visit completed by your child/ward. There will be no charge for study-related doctor visits, examinations, and laboratory tests. All study vaccines will be provided free of charge.

If your child/ward is found to be HIV positive and is eligible for ART treatment, you will be referred to the nearest ART treatment roll-out site. You will be given up to R40.00 as a once off payment in proportion to the distance and return public transport costs to and from the ART treatment site.

Right to ask questions and/or withdraw from the study

If you want any information regarding your child's/ward's rights as a research participant, or complaints regarding this research study, you may contact anyone of these independent committees established to help protect the rights of research participants.

Name of the Chairperson of IEC: _____

Name of the IEC:

Address of IEC:
Tel:

Fax:

If you have any questions about this trial you should first discuss them with your doctor or the ethics committee. After you have contacted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar
SA Medicine Control Council
Department of Health
Private Bag X828 PRETORIA 0001

Personal Doctor / Specialist option

Please indicate below by initialling the appropriate box, whether you want me to notify your child's/ward's personal doctor or your child/ward's specialist of their participation in this study:

☐ YES, I want you to inform my child's/ward's personal doctor/specialist of their participation in this study.

☐ NO, I do not want you to inform my child's/ward's personal doctor/specialist of their participation in this study.

☐ My child/ward does not have a personal doctor/specialist.

Termination of Subjects' Study Participation

Your child's/ward's participation in the study may be stopped for any of the following reasons:

- If you do not follow the study doctor's instructions,
- The study doctor decides it is in the best interest of your child's/ward's health and welfare to discontinue participation in the study,
- There are either not enough subjects interested in participating in the study or the study has reached the required number of subjects,
- GSK Biologicals has decided to stop the study at this site for other reasons not known at this time,
- GSK Biologicals stops enrolling new subjects into study for any reason, and your child/ward is in the screening phase of the study and has not yet been assigned to one of the vaccine groups.

Voluntary Participation and Subjects Right to End Participation

Your child's/ward's participation in this study is voluntary. If you do decide for your child/ward to take part, you will be given this information to keep and be asked to sign this consent form. 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. You must inform your study doctor if you decide to do this. 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.

Any information and results collected before your child's/ward's withdrawal from the study will be used by GlaxoSmithKline.

Confidentiality and Data Privacy

Maintaining confidentiality is important to GlaxoSmithKline Biologicals S. A., WHO and PATH. Your child's/ward's personal information (for example, gender, age, the details of his/her medical conditions) and other information (the data collected by GlaxoSmithKline as part of the study) will be identified by a number (i.e., coded). Information identifying your child will remain confidential and, to the extent permitted by relevant laws and regulations, will not be made publicly available. Your child's/ward's name or any other identifying particulars will not appear in any publications or reports produced from this study.

GlaxoSmithKline Biologicals S. A. will keep the information and the results collected about your child/ward in this study. Your child's/ward's name and address are not included in the information kept by GlaxoSmithKline Biologicals S. A. - only your study doctor will keep this information. GlaxoSmithKline Biologicals S. A. has told your study doctor to keep the information about your child/ward in a secure place. GlaxoSmithKline will comply with internal procedures to protect personal and other information even in countries where data privacy laws are less strict than in Europe/US.

By agreeing to take part in this research study you will be allowing certain persons to see the information about your child/ward (both personal, including his/her name, and other information) held by the study doctor. Your child's/ward's information will be looked at to confirm that it is correct and that it is related to your child/ward. This will be done by selected people working for GlaxoSmithKline and organisations acting on behalf of GlaxoSmithKline Biologicals S. A. are required to maintain the confidentiality of your information.

Your child's/ward's information will be processed electronically (i.e., by a computer) or manually and analysed to determine outcome of this study. GlaxoSmithKline may use your child's/ward's information for other medical/health care purposes related to development of this vaccine. For this purpose only your child's/ward's coded information will be used.

Your child's/ward's information may be sent to regulatory authorities, to the IEC/IRB, to other doctors and/or organisations working with GlaxoSmithKline. It may also be sent to other GlaxoSmithKline sites in this country and in other countries where there may be different or lesser standards for looking after it. GlaxoSmithKline will apply the same standard in the protection of your information to the extent permitted by law.

You have the right to ask the study doctor about the data being collected on your child/ward for the study and about the purpose of this data. You have the right to ask the study doctor to allow you to see your child's/ward's personal information and to have any needed corrections to it made.

Notification of New Information

Sometimes during the course of a research project, new information becomes available about the vaccine that is being studied. If this happens, we will tell you about new information that may affect you and your child/ward's willingness to stay in this study.

Written Informed Consent Form
Study Identification rota-037

Subject ID _____

CONFIDENTIAL

Consent statement

The HUMAN ROTAVIRUS vaccine study has been clearly explained to me and I have read and understood the information provided [A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants in South Africa, Version 4, dated 04/11/2005, 12 pages].

I, _____, the legal representative of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child /ward (subject)

hereby freely give my consent for my child/ward to take part in this [clinical/vaccine] study.

I 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.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to allow my child /ward to take part in this study.

I agree to take part in this study and to my child / ward's participation in this study. I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

I have names of person(s) who I can contact in case of any study-related questions during the study, or if I want to withdraw my child from the study.

***Signature of Legal Representative** _____ **Date:** _____
DD/ MM/ YY

***Printed name of Legal Representative** _____

If the legal representative is illiterate, an Independent Literate Witness should also sign the consent form (if possible, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Signature of Investigator* _____ Date: _____

DD/ MM/ YY

Printed Name Investigator* _____

***only required if the Investigator was not the person conducting the Consent**

Written Informed Consent Form
Study Identification rota-037

Subject ID _____

CONFIDENTIAL

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written consent form.

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Designation of Person conducting Consent _____

Signature of Investigator* _____ Date: _____

DD/ MM/ YY

Printed Name Investigator* _____

***only required if the Investigator was not the person conducting the Consent**

Consent for Storage and Future Use of Leftover Specimens

Collected samples may be stored and used for purposes related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably.

Collected samples may also be made anonymous (meaning that the link between your child/ward and the sample will be destroyed) to be used for other research purposes.

Collected samples may be stored for a long time (up to 15 years) and used for purposes related to the quality assurance of laboratory tests. This may include the set up of new test methodologies as well as making sure that new assays are comparable to previous methods and work reliably. No Genetic Research will be conducted on the stored samples.

You will be asked to complete the consent form, on page 15 of this document, to state your decision.

Written Informed Consent Form
Study Identification rota-037

Subject ID _____

CONFIDENTIAL

If any of the specimens my child/ward has provided for this research project are left over after 15 years (**Please Initial one** choice from each of the following boxes)

- ☐ I wish this leftover material to be destroyed immediately
- ☐ I give permission for this leftover material to be stored and used in future research but only on the same subject as the current research project
- ☐ I give permission for this leftover material to be stored and used in future research of any type.

- ☐ I want this leftover material to be destroyed after ____ years.
- ☐ I give permission for this leftover material to be stored indefinitely

- ☐ I want my identity to be removed from the left over specimens.
- ☐ I want my identity to be kept with the left over specimens

Print Name of Subject

_____

Date and Signature of parent/guardian

_____

___/___/___ (dd/mm/yy)

If illiterate:

Print Name of Independent Literate Witness

Date and Signature of Witness

(ideally, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

_____

_____

___/___/___ (dd/mm/yy)

Person conducting Consent / Researcher:

Print Name of Researcher

_____

Date and Signature of Researcher

_____

___/___/___ (dd/mm/yy)

Investigator:

Print Name of Investigator*

_____

Date and Signature of Investigator*

_____

___/___/___ (dd/mm/yy)

*only required if the Investigator was not the person conducting the Consent

SUMMARY INFORMED CONSENT FOR RE-CONSENTING

Study Identification: 102248 (rota-037)

Study Title: A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.

Version Number: Version 1.4 final **Date:** 22/03/2006

Company Name: GlaxoSmithKline Biologicals S.A.

Subject Identification: Healthy infants who are 5-10 weeks of age at the time of the first dose.

This document should be presented to the subject's parent or guardian in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.

INTRODUCTION

To the mother/legal guardian of study participant,

Previously you have been provided with the information necessary to help you decide on your child/ward's participation in the study with GlaxoSmithKline Biologicals' human rotavirus (HRV) vaccine (ICF: XXXX). As of XXXX, a new version of the Informed Consent is available. To inform you on the changes performed on the informed consent version you have previously signed, we are providing you here with a summary update informed consent. A copy of the updated informed consent will also be provided to you for your record.

SUMMARY

Following request from the [redacted] we would like to inform you that the conduct of the study will obey the 2004 version of the Declaration of Helsinki. A copy may be obtained should you wish to review it.

We would like to inform you that the [redacted] has changed their name to [redacted] (This is only applicable to [redacted]

Subject ID _____

Supplementary Informed Consent for Re-consenting
Study Identification rota-037

CONFIDENTIAL

Be aware that University of Cape Town (UCT) was not involved in the Informed Consent review process.

Consent statement

The aims and procedures of the re-consenting have been clearly explained to me and I have read the information sheet and understand the information provided [Summary Informed Consent for Re-Consenting, Version 1.4, dated 22/03/2006, 6 pages].

I, _____, the legal representative of

_____
Printed name of subject's parent or legal guardian

_____
Printed name of child /ward (subject)

I confirm that I have had the opportunity to ask questions about this re-consenting procedure and I am satisfied with the answers and explanations that have been provided.

I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to sign this re-consenting form.

I will receive the full copy of the informed consent form referred to above, including this signed statement with my signature below.

Consent statement

_____
Printed name of child/ward (subject)

***Signature of Legal Representative** _____ **Date:** _____
DD/ MM/ YY

***Printed name of Legal Representative** _____

If the legal representative is illiterate, an Independent Literate Witness should also sign the consent form (if possible, this person should be selected by the participant's parent/guardian and should have no connection to the research team)

CONFIDENTIAL

Signature of Witness _____ **Date:** _____

DD/ MM/ YY

Printed name of Witness _____

Signature of Person conducting Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of Person conducting Consent _____

Statement by Investigator who conducted the informed consent discussion:

I have carefully explained the nature and demand of this re-consenting process to the person named above and witnessed the completion of the written consent form.

Signature of the Investigator who conducted the Consent _____ **Date:** _____

DD/ MM/ YY

Printed Name of the Investigator who conducted the Consent _____

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 Fax number
Dr. Dr. (sub-I)			Malawi	Phone : Mobile : Dr. Fax : NA
Dr. Dr. (Sub-I)/ Dr. (Sub-I)/ Dr. (Sub-I)			Malawi	Phone : Mobile : Dr. Fax : NA
Dr. Dr. (sub-I)			Malawi	Phone : Mobile : Dr. Fax : NA
Dr. Dr. (Sub-I)/ Dr. (Sub-I)/ Dr. (Sub-I)			Malawi	Phone : Mobile : Dr. Fax : NA
Dr Dr.				Phone: Fax:
Dr Dr.				Phone: Fax:
Dr				Phone: Fax:
Dr				Phone: Fax:

Investigator's name	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]
Dr [redacted]	[redacted]	[redacted]	[redacted]	Phone: [redacted] Fax: [redacted]

* GSK Biologicals' assigned center number

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Signature of principal or coordinating investigator

GlaxoSmithKline Biologicals

Global Clinical Research and Development

Investigator Approval Page

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, safety and immunogenicity of two or three doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine Expanded Program of Immunisation (EPI) vaccinations in healthy infants.

Study: 102248 (Rota-037) 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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aca7ac874065a9230d08a9934d151516 1.1 10/04/2009

GlaxoSmithKline Biologicals
Global Clinical Research and Development

Sponsor Signatory Approval Page

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, safety and immunogenicity of two or three doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine Expanded Program of Immunisation (EPI) vaccinations in healthy infants.

Study: 102248 (Rota-037) 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:

Title of Sponsor Signatory:

Signature: _____

Date: _____

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aca7ac874065a9230d08a9934d151516 1.1 10/04/2009

Listings of patients receiving test drug(s) /investigational product(s) from specific batches

Not applicable.

Randomisation List

As the study is still ongoing, the blinding will be maintained for the whole study period (i.e. end of second efficacy period). The randomisation list will be provided only after complete freezing of the database after the second efficacy period.

AUDIT CERTIFICATE

Report/Submission Number: Rota (102248) / 037

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312).

During the conduct and reporting of this study, the following independent audits were performed by or on behalf of GlaxoSmithKline.

Study Number	Audit Type	Auditor	Centre number	Country	Audit Date
Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	27 March 2006
Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	27 March 2006
Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	27 March 2006
Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	27 March 2006
Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	27 March 2006
Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	27 March 2006
Rota (102248) / 037	Investigator Site	GSK	[redacted]	Malawi	30 August 2007

Rota (102248) / 037	Investigator Site	GSK	[redacted]	South Africa	24 June 2008

Clinical Compliance hereby confirm that the audit detailed above was 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:** 20 January 2009

Global Quality & Compliance
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Documentation of statistical methods

Refer to Section 5.11 of the report.

Documentation of inter-laboratory standardization methods and quality assurance procedures

Not applicable

Publications based on the study

Not applicable.

Important publications referenced in the report

Individual Listings

As the study is still ongoing, the blinding will be maintained for the whole study period (i.e. end of second efficacy period). The individual listings will be provided only after complete freezing of the database after the second efficacy period.

Case report forms (CRFs /eCRFs)

This appendix is provided as 4 separate PDF files

Document Name	Checksum	Version	Created on
ROTA-037 (102248) CRF for SAE 01	449328924e800a8c5ec39981388b6298	1.0	07/04/2009
ROTA-037 (102248) CRF for SAE 02	b800943f894acc04efb10e548c1ccd03	1.0	07/04/2009
ROTA-037 (102248) CRF for SAE 03	bd2a2329deea7a6e1846ca50f196236f	1.0	07/04/2009
ROTA-037 (102248) CRF for SAE 04	c1c3b428ced9fd62a005a1d5c24a9df7	1.0	07/04/2009

This section contained journal publication(s), which are protected by copyright laws and therefore have been redacted.

GlaxoSmithKline

Study Reporting and Analysis Plan Approval

Title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.
eTrack study number	Rota-037 (102248) – 037 EXT Y2 (111274)
Scope:	All data pertaining to the above study
Date:	29-February-2008
Co-ordinating author:	[redacted] (ALL4IT)
Other author(s):	[redacted]

Approved by:

Director, Worldwide Clinical Development, Rota virus 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

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According to Protocol
BCG	Bacille Calmette-Guérin
CI	Confidence Interval
CRF	Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EPI	Expanded Program of Immunisation
GE	Gastroenteritis
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IS	Intussusception
LL	Lower limit
MedDRA	Medical Dictionary for Regulatory Activities
ml	Milliliter
OPV	Oral Poliovirus Vaccine
PCR	Polymerase Chain Reaction
RV	Rotavirus
RVP	Rotavirus Vaccine Program
SAE	Serious Adverse Event
U/ml	Units per milliliter
UL	Upper limit
VE	Vaccine Efficacy

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 ROTA-037 (102248); 037 EXT Y2 (111274) Protocol Administrative Change 2 (30-AUG-2007). The changes in the analyses as compared to the protocol/amendment 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 severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

3.2. Secondary Endpoints

Efficacy endpoints:

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 6.
- In South Africa, occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or

placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.

- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

For subjects in Cohort 2 South Africa and the Cohort in Malawi:

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

Safety endpoints:

- For all subjects, occurrence of AEs/SAEs leading to drop-out throughout the entire study period.
- For all subjects, occurrence of SAEs throughout the entire study period.

Immunogenicity Endpoints:

- In a subset of subjects, seroconversion rate and Geometric Mean concentration (GMC) to anti-rotavirus IgA antibody at Visit 4.
- In all subjects, seropositivity rate and GMC to anti-rotavirus IgA antibody at Visit 4.

3.3. Study cohorts to be evaluated

Total vaccinated cohort

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

- a safety analysis based on the total vaccinated cohort will include all vaccinated subjects.
- an immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects for whom immunogenicity data are available.

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

Total vaccinated cohort for interim analysis

The total vaccinated cohort for interim analysis will include all subjects from Cohort 1 and Cohort 2 in South Africa:

- who received their full study vaccination course
- who have follow-up beyond 2 weeks after the last dose of the study vaccination course

According-to-protocol (ATP) cohort for safety

The ATP cohort for safety will include all vaccinated subjects:

- who have received at least one dose 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.
- who have not received a replacement vial, except if the appropriate vaccine was administered in “double-blind replacement”.

ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects from ATP cohort for safety:

- who received their full study vaccination course.
- who have no RV other than vaccine strain in diarrhoeal stool samples collected between the day of Dose 1 is administered and 2 weeks after the last dose of the study vaccination course.
- who have entered into the efficacy surveillance period:
    - have follow-up beyond 2 weeks after the last dose of the study vaccination course for analysis of the first and combined efficacy follow-up periods.
    - have follow-up beyond the end of the first efficacy follow-up period for analysis of the second efficacy follow-up period.
- who are part of cohort 2 from South Africa or Malawi for the combined efficacy follow-up period

ATP cohort for immunogenicity

The ATP cohort for immunogenicity will include all subjects from the ATP cohort for safety:

- 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 reporting and analysis plan defined age-interval),
- who comply with vaccination schedule for HRV vaccine or placebo (outside reporting and analysis plan defined interval),
- who comply with blood sampling schedule (outside reporting and analysis plan defined interval),
- for whom immunogenicity data are available, at post sampling timepoint.
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 4.
- who have no concomitant infection unrelated to the vaccine which may influence the immune response.

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

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 cohort for safety.

The ATP cohort for immunogenicity 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 with post-vaccination immunological results are excluded from the ATP cohort for immunogenicity. In such a case, the total vaccinated cohort analyses evaluate whether exclusion from the ATP cohort have biased the results.

The list of applicable elimination codes for each cohort is povided in a separate document (refer to Section 6).

Cohort	**Elimination codes**	**Eli Type**
Total vaccinated cohort for interim analysis	1010, 1030, 3010, 3020	IA
ATP cohort for analysis for safety	1010-1070	MA
ATP cohort for analysis for immunogenicity	1010-2500	MA
ATP cohort for analysis of the first efficacy follow-up period	1010-1070 3010-3030	MA
ATP cohort for analysis of the combined efficacy follow-up period	1010-1070 3010-3030 4005	MA
ATP cohort for analysis of the second efficacy follow-up period	1010-1070 3010-3030 4005-4020	MA

3.4. Derived and transformed data

Efficacy

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

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

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting) are calculated by counting the number of days with presence (>0) of looser than normal stool (vomiting). Missing value at a specific day is considered as absence of looser than normal stool (vomiting) at that day.
- The maximum looser than normal stool (vomiting) is defined as the maximum value observed from the number of looser than normal stool (vomiting) recorded daily during the GE episode.
- As the treatment is recorded in the eCRF, score associated to the treatment can then be directly derived from the eCRF.
- As the dehydration is recorded in the eCRF, score associated to the treatment can then be directly derived from the eCRF**.**

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

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

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

VE = vaccine efficacy = (1- RR)*100 = (1 – (ARV/ARU))*100

Where:

ARU = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one severe RV GE episode / total number of subjects in the placebo group.

ARV = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one severe RV GE episode / total number of subjects in the HRV vaccine group.

RR = relative risk = ARV/ARU

Immunogenicity

The cut-off value of anti-rotavirus IgA antibody defined by the laboratory before the analysis and is described in Section 5.6.2.4 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 antibodies (i.e. concentration greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.

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

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

Safety

For the analysis of SAE/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject, missing or non-evaluable HIV measurements will not be replaced. Therefore, a safety analysis based on the HIV seropositivity status will exclude subjects with missing or non-evaluable HIV measurements.

3.5. Data presentation description

The following decimal description will be used for the demography, efficacy, safety 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
	GMC ratio	2

3.6. Group description

The following groups will be used for the statistical analyses.

Study	Group order in tables	Group label in tables (8 characters only)
102248/037	1	HRV_2D
	2	HRV_3D
	3	HRV_POOL
	4	Placebo

The study vaccination regimen is summarised:

Group	Visit 1	Visit 2	Visit 3
HRV_2D	Placebo	HRV	HRV
HRV_3D	HRV	HRV	HRV
Placebo	Placebo	Placebo	Placebo

3.7. Final analyses

Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed after subjects have completed Visit 7, and will be presented in an annex report.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 6. However, access to the individual treatment decode will be provided to the investigators only after the final analyses of the second efficacy follow-up has been performed.

3.7.1. Analysis of demographics/baseline characteristics

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 will be calculated per group. The racial and gender composition will be presented.

HIV status will be presented. HIV status will be defined in an amendment of the RAP as this will not be used for the interim analysis.

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo will be calculated per group. The median, mean, range and standard deviation of age in months at Visits 6 and 7 or at last contact if the study visit was not performed will also be calculated per group.

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

The percentages of subjects who received concomitant and intercurrent vaccinations will be tabulated by group.

3.7.2. Analysis of efficacy

Vaccine efficacy will be calculated by HRV group and for pooled HRV groups, with their 95% CI against:

- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the HRV vaccine or placebo until Visit 6.
- In South Africa, severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

In addition, vaccine efficacy will be calculated, with their 95% CI, against

- severe RV GE caused by the circulating wild-type RV strains, hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE, severe RV GE (G1 and non-G1) for the second and combined efficacy periods and for pooled HRV groups.
- severe RV GE caused by the circulating wild-type RV strains after 3 doses of HRV vaccine versus 2 doses of HRV vaccine for the combined efficacy period.

The primary objective will be reached if the lower limit of the 95% CI on vaccine efficacy for pooled HRV groups against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 is >0%.

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE requiring hospitalisation, efficacy from Dose 1 until 2 weeks after Dose 3 of study vaccination, time to events analysis, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system).

3.7.3. Analysis of safety

The percentage of subjects with SAEs reported during the study period will be tabulated by group according to Medical Dictionary for Regulatory Activities (MedDRA) classification, with its exact 95% CI.

The percentage of subjects with SAEs coded to the various MedDRA preferred terms (PT) categories for “Pneumonia disease” during the study period will be tabulated by group, with its exact 95% CI. “Pneumonia disease” is defined as all Preferred Terms under the SOC 'Infections and infestations ' that contains the word 'pneumonia.

The percentage of subjects with AEs/SAEs leading to subject drop-out will be tabulated by group according to MedDRA classification, with its exact 95% CI.

Exploratory safety analyses will be performed according to the HIV seropositivity status.

The height and weight increase from Visit 1 to Visits 4, 6 and 7 will be summarised by group.

3.7.4. Analysis of immunogenicity

For each treatment group, at each time point that a given antigen is measured,

- Seropositivity/seroconversion rates and their exact 95% CI will be tabulated.
- GMCs and their 95% CI will be calculated.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 4 will be displayed using reverse cumulative curves.

The asymptotic standardised 95% CI for difference in the percentage of subjects who were seropositive for anti-rotavirus IgA antibody concentrations at Visit 4 between each HRV group and placebo group, and between pooled HRV groups and placebo group will be computed.

3.7.5. Methodology for computing CI

All CI will be 2 sided 95% CI.

- The exact 95% CIs for proportion within a group will be calculated from Proc StatXact 7.0 assuming independence between doses. Proc StatXact 7.0 was also used to derive the standardized asymptotic 95% CI for the group difference in proportion [ROBERT G. NEWCOMBE , INTERVAL ESTIMATION FOR THE DIFFERENCE BETWEEN INDEPENDENT PROPORTIONS:

COMPARISON OF ELEVEN METHODS, Statist. Med. 17, 873-890 (1998): the standardized asymptotic method used within GSK Bio is method 6.

- The 95% CI for GMC 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 concentrations were normally distributed with unknown variance. The 95% CI for the GMC 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

An interim analysis on vaccine efficacy against any RV GE and severe RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. The interim analysis will be based on the total vaccinated cohort for the subset of subjects with efficacy follow-up 2 weeks beyond study dose 3. The estimated VE against any wild-type RV GE and severe wild-type RV GE will be provided for the pooled HRV groups versus the placebo group. Distribution of RV GE by serotype will also be available although this will not be provided by group. The interim analysis will be disseminated as described in Section 7.

4. CHANGE FROM PROTOCOL

Rules for dissemination of the interim analysis were set up (refer to Section 7).

The following efficacy endpoints can not be evaluated as it was not recorded in the eCRF if re-hydration therapy was given in a medical facility except if hospitalization occured

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6/7, and from Visit 6 to Visit 7.

5. ANNEX 1: INDIVIDUAL LISTINGS AND TEMPLATE OF TABLES

5.1. Individual listings for the final analysis up to Visit 6

The following individual data listings will be provided:

Appendix Table II.Cii - Serious Adverse Events reported up to Visit 6 for subjects who died before Visit 6 (unblinded)

Appendix Table II.Ciii - Serious Adverse Events reported up to Visit 6 for subjects who do not died before Visit 6 (blinded)

5.2. Individual listings for the final analysis up to Visit 7

The following individual data listings will be provided:

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.D - General medical history - Physical examination

Appendix Table I.Ei - Conclusion

Appendix Table I.F - Height and weight

Appendix Table I.G - Vaccination procedure

Appendix Table I.H - Reason for non-eligibility

Appendix Table II.Ci - Non-serious Adverse Events leading to drop-out

Appendix Table II.Cii - Serious Adverse Events

Appendix Table II.Di - Concomitant medications

Appendix Table II.Dii - Concomitant vaccinations

Appendix Table III.A – Immunogenicity

Appendix Table IV.A - Gastroenteritis stool collection results

Appendix Table VA – Detailed information of GE episodes

Appendix Table VIA – HIV test by Visit

Appendix Table VIB – Detailed information of HIV tests and results

5.3. List of tables for the final analysis

5.3.1. For Demographics Analysis:

TABLE # in reference of section 5.4	Table Title	Interim analysis	Final Analysis	Macro
Table D 1	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts (safety and immunogenicity) with reasons for exclusion	CR£	CR	%ELIMLIST
Table D 2	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for Efficacy with reasons for exclusion		CR	%ELIMLIST
Table D 3	Number of subjects by center (Total vaccinated cohort)		ST	%CENTER
Table D 4	Number of subjects enrolled in each country - Total vaccinated cohort		CR	%Freq_dis
Table D 4	Number of subjects enrolled in each country , for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£		%Freq_dis
Table D 5	Number of subjects at each visit and list of withdrawn subjects up to visit 6 (Total vaccinated cohort)		WT	%DROPOUT
Table D 5	Number of subjects at each visit and list of withdrawn subjects up to visit 7 (Total vaccinated cohort)		WT	%DROPOUT
Table D 6	Number of subjects entered, completed and withdrawn with reason for withdrawal at Visit 6 (Total vaccinated cohort)		CR	%DROP_SUM
Table D 6	Number of subjects entered, completed and withdrawn with reason for withdrawal at Visit 7 (Total vaccinated cohort)		CR	%DROP_SUM
Table D 7	Deviations from specifications for age and intervals between study visits (Total Vaccinated Cohort)		ST	%INT_VAL
Table D 7	Deviations from specifications for age and intervals between study visits (ATP cohort for immunogenicity)		WT	%INT_VAL
Table D 8	Number of days between the 3 doses of HRV vaccine/Placebo (Total vaccinated cohort)		ST	%INT_VAL
Table D 9	Minimum and maximum activity dates (Total vaccinated cohort)		WT	%DATE
Table D 10	Summary of demographic characteristics (Total vaccinated cohort)		ST*$	%DEMOGRA
Table D 10	Summary of demographic characteristics, for	CR£		%DEMOGRA

TABLE # in reference of section 5.4	Table Title	Interim analysis	Final Analysis	Macro
	pooled HRV groups and placebo group (Total vaccinated cohort for interim analysis)			
Table D 10	Summary of demographic characteristics (ATP cohort for Immunogenicity)		ST	%DEMOGRA
Table D 10	Summary of demographic characteristics (ATP cohort for efficacy)		CR	%DEMOGRA
Table D 11	Increase in height and weight from Visit 1 to Visits 4, 6 and 7 (Total vaccinated cohort)		ST$	%FREQ_DIS
Table D 12	Summary of co-administered vaccinations by dose – Total vaccinated cohort		ST$	%FREQ_DIS
Table D 13	Summary of vaccinations other than HRV/placebo administered from birth up to Visit 7, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)		ST$	%FREQ_DIS
Table D 14	Summary of HIV tests and results performed during the study (Total vaccinated cohort)		CR$	%FREQ_DIS
Table CTRS 1	Demography of CTRS – Pooled countries		CTRS	%CTR_DEMOG

CR = Within the clinical report
CR£: clinical report generated if allowed (refer to section 7)
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure
CTRS=table for use in the clinical trial registry summary
$=in addition similar tables will be generated for each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
*: 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

5.3.2. For Reactogenicity Analysis:

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 1	Number and percentage of subjects who received HRV/placebo vaccine dose(s) (Total vaccinated cohort)		CR*	%EXPO
Table R 2	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort		ST	%UNSOL
Table R 2	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST/ CTRS	%UNSOL
Table R 3	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 3	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 4	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort		CR	%UNSOL
Table R 4	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		CR	%UNSOL
Table R 5	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	vaccinated Cohort)			
Table R 5	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort		ST *$	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST*$	%UNSOL
Table R 6	Percentage of subjects reporting SAEs coded to the various MedDRA Preferred Terms categories for “Pneumonia disease” occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (total vaccinated cohort)		ST	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort		ST*	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST*	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST*$	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up		ST*$	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	to Visit 7 - Total vaccinated cohort			
Table R 6	Percentage of subjects reporting SAEs coded to the various MedDRA Preferred Terms categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (total vaccinated cohort)		ST	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST*	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST*	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs coded to the various MedDRA Preferred Terms categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs coded to the various MedDRA Preferred Terms categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort		ST *$	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		CR *$	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST *$	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		CR *$	%UNSOL
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	(SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort			
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 10	Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visits 6 – Total vaccinated cohort		ST	%UNSOL
Table R 10	Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visits 7 – Total vaccinated cohort		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 11	Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities due to “Pneumonia disease” from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities due to “Pneumonia disease” from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities due to “Pneumonia disease” from occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities from Dose 1 of HRV vaccine or placebo up to Visit 6(Total vaccinated Cohort)		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities due to “Pneumonia disease” from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 13	Listing of fatalities from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 13	Listing of fatalities from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group from Dose 1 of HRV vaccine or placebo up		WT	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	to Visit 6 (Total vaccinated cohort)			
Table R 14	Summary of fatalities by dose and group from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV positive subjects from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV negative subjects from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for subjects with unknown HIV status from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV positive subjects from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV negative subjects from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for subjects with unknown HIV status from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV positive subjects with fatalities occurring from Dose 1 of HRV		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	vaccine or placebo up to Visit 6 (Total vaccinated cohort)			
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV negative subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with unknown HIV status fwith fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV positive subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV negative subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with unknown HIV status fwith fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		ST	%UNSOL
Table R 16	Subjects with serious adverse events reported from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%SAE
Table R 16	Subjects with serious adverse events reported after Visit 6 up to Visit 7 (Total vaccinated cohort)		ST	%SAE
Table CTRS 2	Number (%) of subjects with serious adverse events from Dose 1 up to Visit 7(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

$=in addition similar tables will be generated for each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
*: 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.

For the analysis on AEs/SAEs leading to drop-out, the following rules will be applied

Rule 1 : In case of withdrawal of the subject because of death, only SAEs reported in the CIOMS of the SAEs leading to death will be included in the analysis. In other situations, only SAEs reported in the last CIOMS before withdrawal of the subject will be included in the analysis of SAEs leading to drop-out.

Rule 2: Non-SAEs and SAEs with missing or incomplete start date will be kept in the analysis of non-SAEs and SAEs leading to drop-out

5.3.3. For Immunogenicity Analysis:

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis	Macro
Table I 1	Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity)		CR*$/CTRS	%GMT
Table I 1	Anti-rotavirus IgA antibody GMC and seropositivity rates for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Table I 2	Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)		CR*$/CTRS	%GMT
Table I 2	Anti-rotavirus IgA antibody GMC and seroconversion rates for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity)		CR*$	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity)		CR*$	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Figure I 1	Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at visit 4 (ATP cohort for immunogenicity)		ST	%REVCUM ps:logscale=10
Table I 4	Difference between groups in percentage of subjects seropositive for anti-rotavirus IgA antibody at Visit 4 - ATP cohort for immunogenicity		CR	%SP_CI
Table I 5	Ratio of anti-rotavirus IgA antibody GMCs at Visit 4 between HRV groups - ATP cohort for immunogenicity		CR	%BIOGMT

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure
$=in addition similar tables will be generated for each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
*: a complementary analysis based on the Total Vaccinated cohort will be provided if more than 5% of the vaccinated subjects are excluded from that cohort. The resulting tables will appear as supplemental tables.

5.3.4. For Efficacy Analysis

The tables and graphs below will also be done for the period from 2 weeks after dose 3 until Visit 7, for the ATP cohort for efficacy - combined efficacy follow-up period.

The tables and graphs below will also be done for the period from Visit 6 up to Visit 7, for the ATP cohort for efficacy - second efficacy period.

The tables and graphs below will also be done for the period from Dose 1 up to Visit 6, for the Total vaccinated cohort.

The tables and graphs below will also be done for the period from Dose 1 up to Visit 7, for the Total vaccinated cohort. Cox method will be used for the computation of vaccine efficacy.

Only GE episodes in which wild-type RV (i.e. other than the vaccine strain) is identified in a stool specimen will be included in the efficacy analysis, except for Table E1.

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
Table E 1	Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from dose 1 up to Visit 6- 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 3 up to Visit 6 - ATP cohort for efficacy		CR*
Table E 2	Percentage of HIV positive subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 3	Percentage of GE episodes with no available stool results from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST*
Table E 3	Percentage of GE episodes with no available stool results from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£	
Table E 4	Percentage of GE episodes with missing information for the number of looser than normal stools per day during the GE episode from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST
Table E 5	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 by severity using the 20-point Vesikari scale - ATP cohort for efficacy		CR*
Table E 5	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 by severity using the 20-point Vesikari scale for HIV positive subjects - ATP cohort for efficacy		ST
Table E 6	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by severity using the 24-point Clark scale - ATP cohort for efficacy		ST
Table E 7	Percentage of subjects with RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*
Table E 8	Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*
Table E 9	Percentage of subjects who were fully vaccinated (at least 2 weeks after Dose 3) before the beginning of the RV season In South Africa - ATP cohort for efficacy		ST
Table E 10	Number of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*$
Table E 10	Number of RV GE episodes reported from 2 weeks after	CR£	

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
	Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, by G serotype and P genotype and for pooled groups - Total vaccinated cohort for interim analysis		
Table E 11	Number of severe RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*$
Table E 12	Characteristics (based on Vesikari scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy		ST
Table E 12	Characteristics (based on Vesikari scale) of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 13	Characteristics (based on Clark scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy		ST
Table E 13	Characteristics (based on Clark scale) of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 14	Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST*$
Table E 14	Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£	
Table E 15	Percentage of subjects reporting RV GE and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		CR *$/CTRS
Table E 15	Percentage of subjects reporting RV GE and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£	
Table E 16	Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - ATP cohort for efficacy		ST
Table E 17	Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		CR *$/CTRS
Table E 17	Percentage of subjects with severe RV GE episodes and efficacy during the period from 2 weeks after Dose 3 up to Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks after Dose 3) before the beginning of the RV season In South Africa - ATP cohort for efficacy		ST/CTRS
Table E 17	Percentage of subjects with severe RV GE episodes and efficacy during the period from 2 weeks after Dose 3 up to Visit 6 for the subset of subjects who were fully vaccinated		ST

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
	(at least 2 weeks after Dose 3) after the beginning of the RV season In South Africa - ATP cohort for efficacy		
Table E 17	Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis efficacy	CR£	
Table E 18	Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - ATP cohort for efficacy		ST/CTRS
Table E 19	Percentage of subjects reporting RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 20	Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST$
Table E 21	Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - ATP cohort for efficacy		ST
Table E 22	Percentage of subjects reporting RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 23	Percentage of subjects reporting all cause GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST$
Table E 23	Percentage of subjects reporting all cause severe GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		CR$/CTRS
Table E 24	Percentage of subjects hospitalized and/or treated with re-hydration therapy due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST/CTRS
Table E 24	Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 - ATP cohort for efficacy		CR
Table E 25	Percentage of subjects hospitalized and/or treated with re-hydration therapy due to GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 25	Percentage of subjects hospitalized due to GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 - ATP cohort for efficacy		ST

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
Table E 26	Percentage of subjects reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by status of anti-rotavirus IgA antibody concentration after Dose 3 - ATP cohort for efficacy		ST
Table E 26	Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by status of anti-rotavirus IgA antibody concentration after Dose 3 - ATP cohort for efficacy		ST
Table E 27	Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by Cox - ATP cohort for efficacy		ST
Figure E 1	Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 2	Distribution of Clark score for RV GE reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 3	Seasonal distribution of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy		ST$
Figure E 4	Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy		ST$
Figure E 5	Efficacy of the vaccine against RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 6	Efficacy of the vaccine against RV GE episodes with a score ≥X on the Clark scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 7	The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST
Figure E 7	The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST
Figure E 7	The Kaplan Meier curve for severe RV GE due to non-G1 serotypes from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST

CR = Within the clinical report
CR£: clinical report generated if allowed (refer to section 7)
ST = As a supplementary table or figure
WT = As a working table or figure
$ = In addition similar tables will be generated by each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
* = In addition similar tables will be generated for the analysis from dose 1 of HRV/placebo up to 14 post dose 3 of HRV/placebo and from dose 1 of HRV/placebo up to before dose 3 of HRV/placebo on the total vaccinated cohort

5.4. Template of tables

Table D 1 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts (safety and immunogenicity) with reasons for exclusion

	Total			HRV_2D		HRV_3D		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Number of vaccines prepared									
Subjects or vaccine number not allocated (code 1010)									
Total enrolled cohort									
Total vaccinated cohort									
Randomisation code broken at the investigator site (code 1060)									
Study vaccine dose not administered according to protocol (code 1070)									
ATP cohort for safety									
Protocol violation (inclusion/exclusion criteria) (code 2010)									
Administration of any medication forbidden by the protocol (code 2040)									
Underlying medical condition forbidden by the protocol (code 2050)									
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)									
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)									
Essential serological data missing (code 2100)									
Subjects with incomplete vaccination schedule but with post serological result (code 2500)									
ATP cohort for immunogenicity									

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
Data source = Appendix table IA

Table D 2 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for Efficacy with reasons for exclusion

	Total			HRV_2D		HRV_3D		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Number of vaccines prepared									
Subjects or vaccine number not allocated (code 1010)									
Total enrolled cohort									
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 efficacy follow-up period(code 3020)									
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 3 which may influence efficacy response (code 3030)									
ATP cohort for efficacy - first period (Code 4005) Subjects not planned in the protocol to be part of the second efficacy follow-up period **ATP cohort for efficacy - combined period** (Code 4020) Subjects not entered into the surveillance period of the second efficacy follow-up period **ATP cohort for efficacy - 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 cohort for efficacy for the first efficacy follow-up period include all vaccinated subjects with no elimination codes beginning with one thousand or three thousand. The ATP cohort for efficacy for combined efficacy follow-up periods include all vaccinated subjects with no elimination codes beginning with one thousand or three thousand or with elimination code 4005. The ATP cohort for efficacy for the second efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one thousand, three thousand or four thousand.
Data source = Appendix table IA

Table D 3 Number of subjects by center (Total vaccinated cohort)

	HRV_2D	HRV_3D	Placebo	Total	
Center	**n**	**n**	**n**	**n**	**%**
All					

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 x 100
Center = GSK Biologicals assigned center number
Data source = Appendix table IB

Table D 4 Number of subjects enrolled in each country - Total vaccinated cohort

	HRV_2D	HRV_3D	Placebo	Total	
Country	**n**	**n**	**n**	**n**	**%**
South Africa (cohort 1)	XXX	XXX	XXX	XXX	XX.x
South Africa (cohort 2)					
Malawi					

N = number of subjects enrolled in the considered group or in total (sum of both groups)
n/% = number/ percentage of subjects enrolled in each group or in total for a given country.
Data source = Appendix table IB

Table D 5 Number of subjects at each visit and list of withdrawn subjects up to visit 6 (Total vaccinated cohort)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
HRV_2D	VISIT1	Xxx		
			no. xxx	MIGRATION FROM STUDY AREA
			no. xxx	MIGRATION FROM STUDY AREA
	VISIT2	Xxx		
			no. xxx	CONSENT WITHDRAWAL
			no. xxx	MIGRATION FROM STUDY AREA
			no. xxx	MIGRATION FROM STUDY AREA
			no. xxx	MIGRATION FROM STUDY AREA
	VISIT3	Xxx		
			no. xxx	MIGRATION FROM STUDY AREA
	VISIT4	Xxx		
			no. xxx	Xxx
	VISIT5	Xxx		
			no. xxx	Xxx
	VISIT6	Xxx		
			no. xxx	Xxx
HRV_3D	VISIT1	Xxx		
			no. xxx	Xxx
	VISIT2	Xxx		
			no. xxx	Xxx
	VISIT3	Xxx		
			no. xxx	Xxx
	VISIT4	Xxx		
			no. xxx	Xxx
	VISIT5	Xxx		
			no. xxx	Xxx
	VISIT6	Xxx		
			no. xxx	Xxx
Pacebo	VISIT1	Xxx		
			no. xxx	Xxx
	VISIT2	Xxx		
			no. xxx	Xxx
	VISIT3	Xxx		
			no. xxx	Xxx
	VISIT4	Xxx		
			no. xxx	Xxx
	VISIT5	Xxx		
			no. xxx	Xxx
	VISIT6	Xxx		
			no. xxx	Xxx

Data source = Appendix table ICi, Appendix table IEi

Table D 6 Number of subjects entered, completed and withdrawn with reason for withdrawal at Visit 6 (Total vaccinated cohort)

	Group			
	HRV_2D	**HRV_3D**	**Placebo**	**Total**
Number of subjects vaccinated	1600	1600	1600	4800
Number of subjects completed	Xxx	Xxx	Xxx	Xxx
Number of subjects withdrawn	Xxx	Xxx	Xxx	Xxx
Reasons for withdrawal :				
Serious Adverse Event	Xxx	Xxx	Xxx	Xxx
Non-serious adverse event	Xxx	Xxx	Xxx	Xxx
Protocol violation	Xxx	Xxx	Xxx	Xxx
Consent withdrawal (not due to an adverse event)	Xxx	Xxx	Xxx	Xxx
Migrated/moved from study area	Xxx	Xxx	Xxx	Xxx
Lost to follow-up (subjects with incomplete vaccination course)	Xxx	Xxx	Xxx	Xxx
Lost to follow-up (subjects with complete vaccination course)	Xxx	Xxx	Xxx	Xxx
Others	xxx	Xxx	Xxx	Xxx

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed visit 6
Withdrawn = number of subjects who did not come for the visit 6
Data source = Appendix table IEi

Table D 7 Deviations from specifications for age and intervals between study visits (Total Vaccinated Cohort)

		Age at Dose 1 of HRV/placebo	**Dose 1 of HRV/placebo – Dose 2 of HRV/placebo**		**Dose 2 of HRV/placebo – Dose 3 of HRV/placebo**		**Dose 3 of HRV/placebo – BL at Visit 4**	
GROUP		**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 35 to 76 days	from 28 to 48 days	from 21 to 48 days	from 28 to 48 days	from 21 to 48 days	from 30 to 48 days	from 21 to 48 days
HRV_2D	**N**	1890	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	n	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	%	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	range	X to x	X to x	X to x	X to x	X to x	X to x	X to x
HRV_3D	**N**	1890	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	n	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	%	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	range	X to x	X to x	X to x	X to x	X to x	X to x	X to x
Placebo	**N**	1890	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	n	Xxx	Xxx	Xxx	xxx	xxx	xxx	xxx
	%	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	range	X to x	X to x	X to x	X to x	X to x	X to x	X to x

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
BL= blood sample
Data source = Appendix table IB, Appendix table ICi

Table D 8 Number of days between the 3 doses of HRV vaccine/Placebo (Total vaccinated cohort)

	HRV_2D	HRV_3D	Placebo	Total
Number of days between Dose 1 and Dose 2 of HRV vaccine/placebo				
N	XXX			
Mean	XX.x			
SD	XX.xx			
Minimum	XX			
Q1	XX.x			
Median	XX.x			
Q3	XX.x			
Maximum	XX			
Number of days between Dose 2 and Dose 3 of HRV vaccine/placebo				
N	XXX			
Mean	XX.x			
SD	XX.xx			
Minimum	XX			
Q1	XX.x			
Median	XX.x			
Q3	XX.x			
Maximum	XX			

N for number of days between Dose 1 and Dose 2: N= Number of subjects with dose 1 and dose 2 administered
N for number of days between Dose 2 and Dose 3: N= Number of subjects with dose 2 and dose 3 administered
Q1 = 25th percentile
Q3 = 75th percentile
SD = standard deviation
Data source= Appendix Table ICi

Table D 9 Minimum and maximum activity dates (Total vaccinated cohort)

Activity number	Visit Number	Minimum date	Maximum date

Table D 10 Summary of demographic characteristics (Total vaccinated cohort)

Characteristics	Parameters or Categories	HRV_2D N=		HRV_3D N=		Placebo N=		Total N=	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (Weeks) at Dose 1 of HRV vaccine/placebo	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (Weeks) at Dose 2 of HRV vaccine/placebo	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (Weeks) at Dose 3 of HRV vaccine/placebo	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (months) at Visit 6 or at last Contact if visit 6 not performed	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (months) at Visit 7 or at last Contact if visit 7 not performed	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Gender	Female								
	Male								
Race	African heritage / African american								
	American Indian or Alaska Native								
	Asian – Central/South Asian heritage								
	Asian – East Asian heritage								
	Asian – Japanese heritage								
	Asian – South East Asian heritage								
	Native Hawaiian or Other Pacific Islander								
	White – Arabic / North African heritage								
	White – Caucasian / European heritage								
	Other								
Height at visit 1 (cm)	Mean								
	Sd								
	Median								
Weight at visit 1 (kg)	Mean								
	Sd								
	Median								
BMI at visit 1	Mean								

(kg/m²)	**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 (Weeks) = age expressed in weeks
Data source = Appendix table IB

Table D 11 Increase in height and weight from Visit 1 to Visits 4, 6 and 7 (Total vaccinated cohort)

Visit	**Characteristics**	**Parameters or Categories**	**HRV_2D N=**	**HRV_3D N=**	**Placebo N=**	**Total N=**
			Value	**Value**	**Value**	**Value**
Visit 4	**Increase in height (cm) from Visit 1**	**Mean**	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
	Increase in weight (kg) from Visit 1	**Mean**	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
Visit 6	**Increase in height (cm) from Visit 1**	**Mean**	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
	Increase in weight (kg) from Visit 1	**Mean**	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
Visit 7	**Increase in height (cm) from Visit 1**	**Mean**	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
	Increase in weight (kg) from Visit 1	**Mean**	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Data source = Appendix table IB

Table D 12 Summary of co-administered vaccinations by dose – Total vaccinated cohort

Category	HRV_2D N=		HRV_3D N=		Placebo N=		Total N=	
	n	%	n	%	n	%	n	%
Dose1								
Any								
BCG								
DTPw-HB								
HIB								
OPV								
Dose 2								
	HRV_2D		HRV_3D		Placebo		Total	
	N=		N=		N=		N=	
	n	%	n	%	n	%	n	%
Any								
BCG								
DTPw-HB								
HIB								
OPV								
Dose 3								
	HRV_2D		HRV_3D		Placebo		Total	
	N=		N=		N=		N=	
	n	%	n	%	n	%	n	%
Any								
BCG								
DTPw-HB								
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
Data source = Appendix table I.Ci and II.Dii

Table D 13 Summary of vaccinations other than HRV/placebo administered from birth up to Visit 7, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)

Before Dose 1												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 1 and Dose 2§												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 2 and Dose 3*												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 3 and Visit 6µ												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 3 and Visit 7£												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo
Between Dose 3 and Visit 6: total number of subjects having received dose 3 of HRV/placebo
Between Dose 3 and Visit 7: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered

µ= up to last contact if Visit 6 was not done

£= up to last contact if Visit 7 was not done

Data source= Appendix table I.Ci and II.Dii

Table D 14 Summary of HIV tests and results performed during the study (Total vaccinated cohort)

HIV status during the study	HRV_2D		HRV_3D		Placebo		Total	
	N=		N=		N=		N=	
	n	%	n	%	n	%	n	%
HIV Test								
	N'=		N'=		N'=		N'=	
	n'	%	n'	%	n'	%	n'	%
Positive Negative Unknown								

N = total number of subjects
n/% = number / percentage of subjects tested for HIV
N' = total number of subjects tested for HIV
n'/% = number / percentage of subjects in a given category

Table R 1 Number and percentage of subjects who received HRV/placebo vaccine dose(s) (Total vaccinated cohort)

Total number Of doses received	HRV_2D (N = XXX)		HRV_3D (N = XXX)		Placebo (N = XXX)		Total (N = XXX)	
	n	%	n	%	n	%	n	%
0	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
1	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
2	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
3	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

N = number of subjects in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses in each group or in total
Any = number and percentage of subjects receiving at least one dose
Appendix Table I.C.

Table R 2 Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort

	HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 3 Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

	Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo)			
		95% CI				**95% CI**				**95% CI**		
Primary System Organ Class (CODE)	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*												

At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
%= percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 4 Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort

		HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**Preferred term (CODE)**	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*	*(each Preferred term)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA Preferred Term
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 5 Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

		Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo			
			95% CI				**95% CI**				**95% CI**		
Primary System Organ Class (CODE)	**Preferred term (CODE)**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*	*(each Preferred term)*												

At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA Preferred Term
%= percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 6 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort

	HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified SAE
At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA SOC
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 7 Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

	Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo)			
		95% CI				**95% CI**				**95% CI**		
Primary System Organ Class (CODE)	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*												

At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA SOC
%= percentage of subjects reporting at least once the specified SAE
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified SAE after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 8 Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort

		HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**Preferred term (CODE)**	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*	*(each Preferred term)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified SAE
At least one symptom = number of subjects reporting at least one the specified SAE, whatever the MedDRA Preferred Term
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 9 Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

		Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo			
			95% CI				**95% CI**				**95% CI**		
Primary System Organ Class (CODE)	**Preferred term (CODE)**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*	*(each Preferred term)*												

At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA Preferred Term
%= percentage of subjects reporting at least once the specified SAEs
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified SAE after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 10 Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visits 6 – Total vaccinated cohort

PID	Date of birth	Country	IS type (suspected/probable/possible)	Gender	Age at dose 1 (weeks)	Age at dose 2 (weeks)	Age at dose 3 (weeks)	Age at the start day of the symptom	Previous Dose	Onset day (start date of the symptom)

Table R 11 Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort

		HRV_2D N =				HRV_3D N =				Placebo N =			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom													
(each SOC)	*(each Preferred term)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting the fatal specified symptom
At least one symptom = number of subjects who died during the specified period, whatever the MedDRA Preferred Term
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 12 Statistical comparisons between groups for the percentage of subjects with fatalities due to "Pneumonia disease" from occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

	Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo			
		95% CI				95% CI				95% CI		
Primary System Organ Class (CODE)	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
Pneumonia disease												

%= percentage of subjects reporting at least one "Pneumonia Disease" related to death
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified "Pneumonia Disease" related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 13 Listing of fatalities from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

Group	dose	Day since last dose	Pid	Case Id	Sex	HIV	Day since dose 1	date of death	Age at death (days)	full treatment	Verbatim

Table R 14 Summary of fatalities by dose and group from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

Dose	Group	number of fatalities

Table R 15 Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

HRV_POOL over Placebo			
	95% CI		
RR	LL	UL	P-value

RR= relative risk
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = two-sided exact p_value adjusted for the dose effect for the null hypothesis that the relative risk equals one (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 16 Subjects with serious adverse events reported from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

Pid	Case Id	Age (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome

MA = medical attention
HO = hospitalization
Dose = Dose given prior to the start of the SAE
Day of onset = Number of days since last vaccine dose
Data source = Appendix table IIC

Table I 1 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity)

Group	Timing	N	>= 20 U/ML				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_2D	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

GMC = geometric mean antibody concentration calculated on all subjects
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
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Individual subjects data can be found in Appendix IIIA

Table I 2 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

Group	Timing	N	>= 20 U/ML				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_2D	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

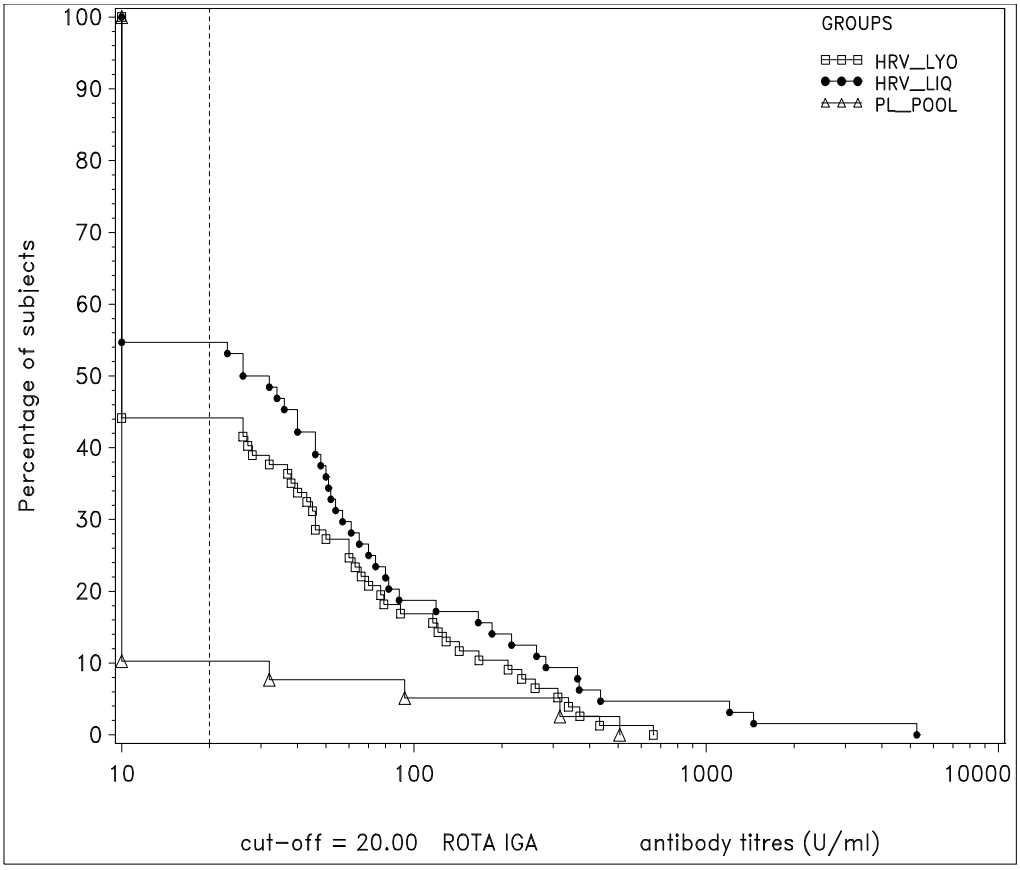
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post timepoints
n/% = number/percentage of subjects who seroconverted
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Individual subjects data can be found in Appendix IIIA

Table I 3 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity)

Group	Timing	N	GMC		
			Value	95% CI	
				LL	UL
HRV_2D	PRE	Xxx	Xxx	Xxx	Xxx
	PIII(M3)				
HRV_3D	PRE	Xxx	Xxx	Xxx	Xxx
	PIII(M3)				
HRV_POOL	PRE	Xxx	Xxx	Xxx	Xxx
	PIII(M3)				
Placebo	PRE				
	PIII(M3)				

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Individual subjects data can be found in Appendix IIIA

Figure I 1 Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at visit 4 (ATP cohort for immunogenicity)



Data Source= Appendix Table III.A

Table I 4 Difference between groups in percentage of subjects seropositive for anti-rotavirus IgA antibody at Visit 4 - ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
HRV_2D			Placebo			HRV_2D - Placebo			
HRV_3D			Placebo			HRV_3D - Placebo			
HRV_POOL			Placebo			HRV_POOL - Placebo			
HRV_3D			HRV_2D			HRV_3D - HRV_2D			

N = number of subjects with available results
% = percentage of subjects who were were seropositive
95%CI = asymptotic standardized 95% confidence interval; LL = lower limit; UL = upper limit
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Source: Appendix III.A

Table I 5 Ratio of anti-rotavirus IgA antibody GMCs at Visit 4 between HRV groups - ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
HRV_3D			HRV_2D			HRV_3D / HRV_2D			

N = number of subjects with available results
95% CI LL, UL: 95% lower and upper confidence interval limits (one-way ANOVA model)
L.L. = lower limit, U.L. = upper limit

Table E 1 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from dose 1 up to Visit 6- Total vaccinated cohort

Group	N	n	%	95%CI	
				LL	UL
HRV_2D HRV_3D HRV_POOL Placebo					

N = number of subjects included in each group
n/% = number/percentage of subjects with vaccine virus in at least one stool sample collected in case of GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
Data Source= Appendix Table V.A

Table E 2 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

Event	Total number of episodes reported	HRV_3D		HRV_2D		HRV_POOL		Placebo	
		n	%	n	%	n	%	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 episode
Data Source = Appendix Table IV.A and V.A

Table E 3 Percentage of GE episodes with no available stool results from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy

Category	HRV_2D		HRV_3D		HRV_POOL		Placebo		Total	
	n	%	n	%	n	%	n	%	n	%
	N'=		N'=		N'=		N'=		N'=	
No stools collected Stools collected but no results available										
No stool results available										

N'= number of GE episodes reported
n/%= number/percentage of GE episodes reported within the specified category
Data Source = Appendix Table V.A

Table E 4 Percentage of GE episodes with missing information for the number of looser than normal stools per day during the GE episode from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy

HRV_2D N'=		HRV_3D N'=		HRV_POOL N'=		Placebo N'=		Total N'=	
n	%	n	%	n	%	n	%	n	%

N'= number of GE episodes reported
n/%= number/percentage of GE episodes reported with a maximum number of looser than normal stool per day during the episodes <3 or missing
Data Source = Appendix Table V.A

Table E 5 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 by severity using the 20-point Vesikari scale - ATP cohort for efficacy

Event	Severity using the 20-point Vesikari scale	HRV_2D		HRV_3D		HRV_POOL		Placebo	
		n	%	n	%	n	%	n	%
GE	Mild (1-6) Moderate (7-10) Severe (≥11) Any								
RV GE	Mild (1-6) Moderate (7-10) Severe (≥11) Any		-						

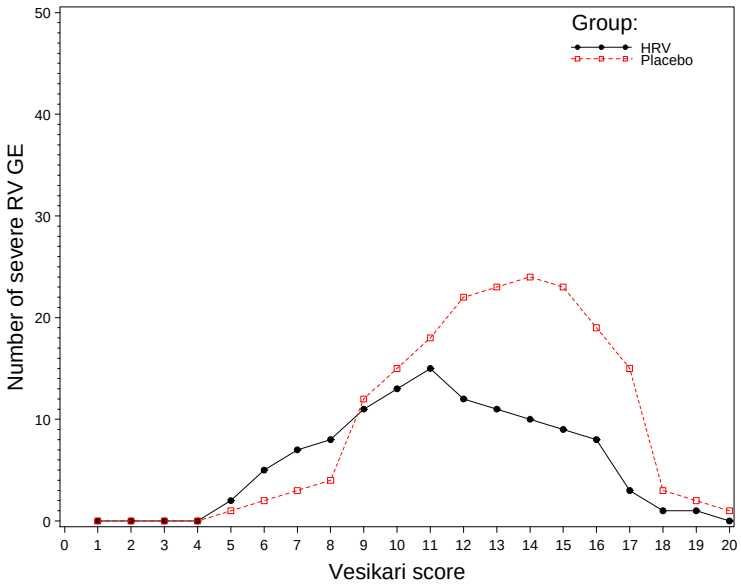
n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported during the considered efficacy period
Any = any specified symptom reported, regardless of Vesikari severity scale
Data Source = Appendix Table IV.A and V.A

Table E 6 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by severity using the 24-point Clark scale - ATP cohort for efficacy

Event	Severity using Clark scale	HRV_2D		HRV_3D		HRV_POOL		Placebo	
		n	%	n	%	n	%	n	%
GE	Mild (1-8)								
	Moderate (9-16)								
	Severe (≥17)								
	Unknown								
	Any								
RV GE	Mild (1-8)								
	Moderate (9-16)								
	Severe (≥17)								
	Any								

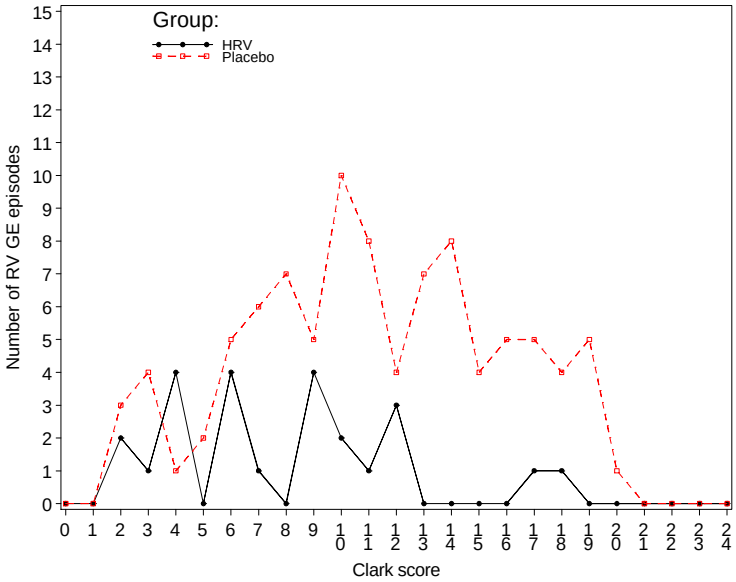
n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported
Any = any specified symptom reported, regardless of Clark severity scale
Data Source = Appendix Table IV.A,and V.A

Figure E 1 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A

Figure E 2 Distribution of Clark score for RV GE reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A

Table E 7 Percentage of subjects with RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

	HRV_2D		HRV_3D		HRV_POOL		Placebo	
Serotype	n	%	n	%	n	%	n	%
	N=		N=		N=		N=	
Any								
G1/P8								
G2/P4								
….								

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype
Any = number of subjects reporting at least one RV GE episode, whatever the serotype
Data Source= Appendix Table IVA and V.A

Table E 8 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

	HRV_2D		HRV_3D		HRV_POOL		Placebo	
Serotype	n	%	n	%	n	%	n	%
	N=		N=		N=		N=	
Any								
G1/P8								
G2/P4								
….								

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype
Any = number of subjects reporting at least one severe RV GE episode, whatever the serotype
Data Source= Appendix Table IVA and V.A

Table E 9 Percentage of subjects who were fully vaccinated (at least 2 weeks after Dose 3) before the beginning of the RV season In South Africa - ATP cohort for efficacy

		HRV_2D		HRV_3D		Placebo	
		N=		N=		N=	
Country	Vaccinated before the RV season	n	%	n	%	n	%
South Africa cohort 1	Yes						
	No						
South Africa cohort 2	Yes						
	No						
South Africa	Yes						
	No						

N = number of subjects included in each group
n/%= number/percentage of subjects in the specified category

Table E 10 Number of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV_2D		HRV_3D		HRV_POOL		Placebo	
	n	%	n	%	n	%	n	%
(each country and overall)	N'=		N'=		N'=		N'=	
G1 wild type G2 G4 and G9 ….								

N'= number of RV GE episodes reported
n/%= number/percentage of RV GE episodes reported, by serotype
Data Source= Appendix Table IVA and V.A

Table E 11 Number of severe RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV_2D		HRV_3D		HRV_POOL		Placebo	
	n	%	n	%	n	%	n	%
(each country and overall)	N'=		N'=		N'=		N'=	
G1 wild type G2 G4 and G9 ….								

N'= number of severe RV GE episodes reported
n/%= number/percentage of severe RV GE episodes reported, by serotype
Data Source= Appendix Table IVA and V.A

Table E 12 Characteristics (based on Vesikari scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy

			HRV_2D		HRV_3D		Placebo	
			N'=		N'=		N'=	
Serotype	Characteristics	Parameters or categories	Value or n	%	Value or n	%	Value or n	%
		N'		-		-		-
(Main serotype and overall)	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 looser 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 RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation
Data Source= Appendix Table IVA and V.A

Table E 13 Characteristics (based on Clark scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV_2D		HRV_3D		HRV_POOL		Placebo	
		N'=		N'=		N'=		N'=	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean SD Median Minimum Maximum								
Duration of looser than normal stools (days)	0 day 1-4 days 5-7 days > 7 days								
Maximum number of looser than normal stools/24 hours	0 2-4 5-7 > 7								
Duration of vomiting (days)	0 - 1 day 2 days 3-5 days > 5 days								
Maximum number of episodes of Vomiting/24 hours	0 1-3 4-6 > 6								
Duration of fever (days)	0 day 1-2 day 3-4 days ≥ 5 days								
Maximum fever reported /24 hours (measured rectally)	< 38.0°C 38.0-38.2°C 38.3-38.7°C ≥ 38.8°C								
Duration of behavioral symptoms	0 day 1-2 days 3-4 days ≥ 5 days								
Behavioral symptoms	Behave as usual Irritable/less playful Lethargic/listless Seizures								

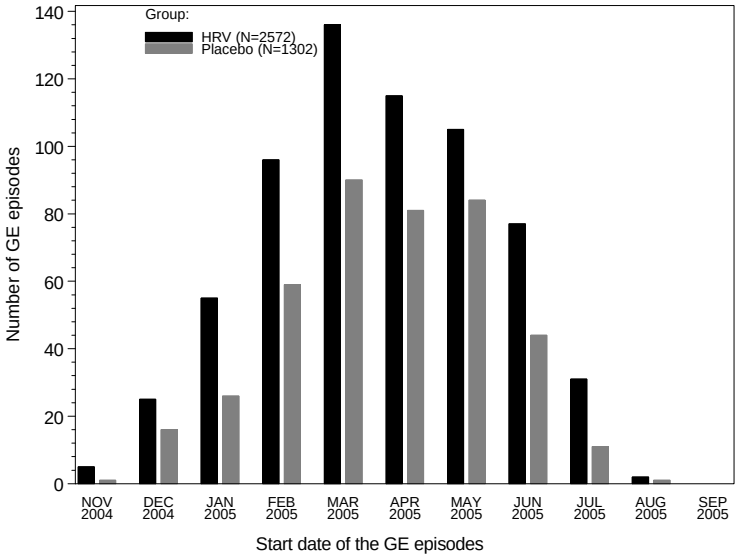
N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation
Data Source= Appendix Table IVA and V.A

Table E 14 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy

Duration (years) of follow-up period	HRV_2D	HRV_3D	HRV_POOL	Placebo
	N=	N=	N=	N=
Total Mean Minimum Q1 Median Q3 Maximum				

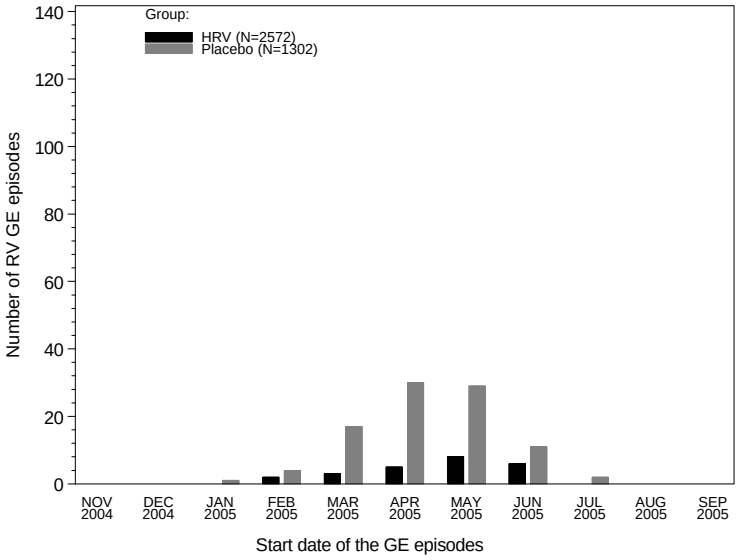
N= Number of subjects included in each group
Total= sum of follow-up period expressed in year
Q1 = 25th percentile
Q3 = 75th percentile
Data Source: Appendix I.Ci

Figure E 3 Seasonal distribution of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy



N = number of subjects included in each group
Data Source= Appendix Table V.A

Figure E 4 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy



N = number of subjects included in each group
Data Source= Appendix Table IVA and V.A

Table E 15 Percentage of subjects reporting RV GE and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

	n/N					Vaccine Efficacy			P-Value
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

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
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 16 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - 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_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
G2	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
…….	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
P8	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Pooled Non G1 (G2, …….)	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source = Appendix Table IV.A and V.A

Table E 17 Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 18 Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - 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_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
G2	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
.....	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Pooled Non G1 (G2, ...)	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source = Appendix Table IV.A and V.A

Table E 19 Percentage of subjects reporting RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

Severity using Vesikari scale	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
≥11	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥12	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥13	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥14	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥15	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥16	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥17	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥18	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥19	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥20	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group

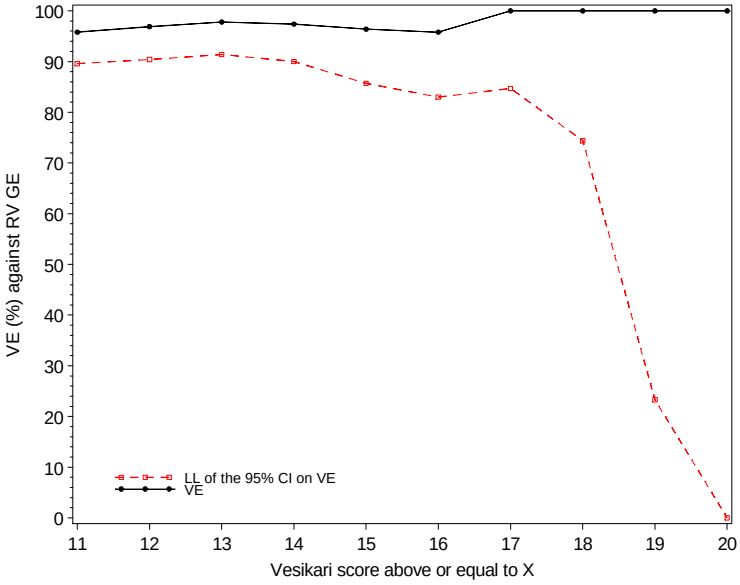
n/% = number/percentage of subjects reporting at least one RV GE episode with a score ≥X on the Vesikari scale, in each group

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

p_value=two-sided exact p_value conditional to the number of episodes

Data Source= Appendix Table IVA and V.A

Figure E 5 Efficacy of the vaccine against RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A
Y-axis has been cut at 0

Table E 20 Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 21 Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - 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_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
G2	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
.....	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Pooled Non G1 (G2, ...)	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source = Appendix Table IV.A and V.A

Table E 22 Percentage of subjects reporting RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

Severity using Clark scale	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
≥17	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥18	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥19	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥20	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥21	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥22	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥23	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥24	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group

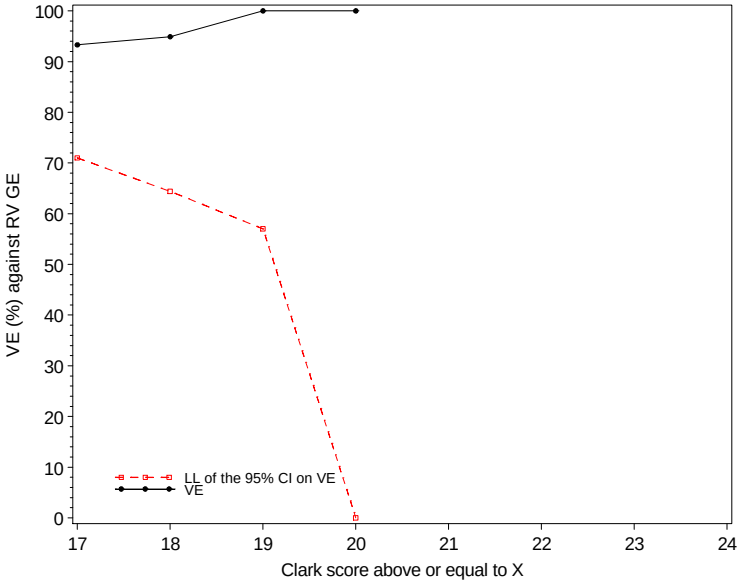
n/% = number/percentage of subjects reporting at least one RV GE episode with a score ≥X on the Clark scale, in each group

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

p_value=two-sided exact p_value conditional to the number of episodes

Data Source= Appendix Table IVA and V.A

Figure E 6 Efficacy of the vaccine against RV GE episodes with a score ≥X on the Clark scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A
Y-axis has been cut at 0

Table E 23 Percentage of subjects reporting all cause GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
South Africa	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
All countries	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group in each country or overall
n/% = number/percentage of subjects reporting at least one GE episode regardless of any cause in each group
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table V.A

Table E 24 Percentage of subjects hospitalized and/or treated with re-hydration therapy due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized and/or treated with re-hydration therapy due to RV GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 25 Percentage of subjects hospitalized and/or treated with re-hydration therapy due to GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized and/or treated with re-hydration therapy due to GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table V.A

Table E 26 Percentage of subjects reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by status of anti-rotavirus IgA antibody concentration after Dose 3 - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 4	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Positive	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Negative	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Unknown	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

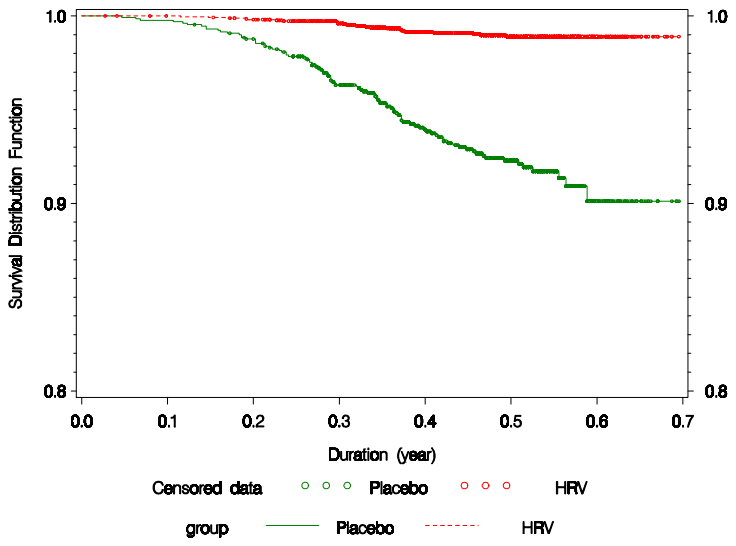
N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode, by status of anti-rotavirus IgA antibodies concentrations at Visit 4
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 27 Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by Cox - ATP cohort for efficacy

Group	N	n	T (year)	n/T value	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Severe RV GE of any wild gtype										
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx				
Severe RV GE of G1 wild type										
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx				
Severe RV GE of pooled Non G1 (G2, G3, G4, ...)										
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx				

N = number of subjects included in each group
n = number of subjects reporting at least one specofoed severe RV GE episode
T= sum of follow-up period expressed in year censored at the first occurrence of sepecified severe RV GE episode
n/T= person-year rate of RV GE in each group
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit
Data Source= Appendix Table IVA and V.A

Figure E 7 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A

Table CTRS 1 Demography of CTRS – Pooled countries

Number of subjects	**HRV_2D**	**HRV_3D**	**Placebo**
Planned, N	Xxx	Xxx	Xxx
Randomised, N (Total Vaccinated Cohort)	Xxx	Xxx	Xxx
Completed, n (%)	Xxx	Xxx	Xxx
Total Number Subjects Withdrawn, n (%)	Xxx	Xxx	Xxx
Withdrawn due to Adverse Events, n (%)	Xxx	Xxx	Xxx
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	Xxx	Xxx	Xxx
Demographics	**HRV_2D**	**HRV_3D**	**Placebo**
N (Total Vaccinated Cohort)	Xxx	Xxx	Xxx
Females:Males	Xxx	Xxx	Xxx
Mean Age, months (SD)	Xxx	Xxx	Xxx
White/caucasian, n (%)	Xxx	Xxx	Xxx

Table CTRS 2 Number (%) of subjects with serious adverse events from Dose 1 up to Visit 7(Total vaccinated cohort)

All SAEs	**HRV_2D N = XXX**	**HRV_3D 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_3D N = XXX**	**HRV_2D N =XXX**	**PLACEBO N =XXX**
Subjects with any SAE(s), n(%) [n related]			

6. ANNEX 2: CRITERIA FOR ELIMINATING SUBJECTS FROM STAT ANALYSES

Provided as a separate document.

7. ANNEX 3: INTERIM ANALYSIS ROTA-037

7.1. Introduction

It is proposed to perform an interim analysis on the 2 South Africa cohorts on data as cleaned as possible. The results of the interim analysis will be shared within GSK and with PATH according to pre-specified criteria (see section 7.3, below). In the scenarios where the results are shared within GSK and with PATH, they will also be shared with external stakeholders and decision-makers (e.g., GAVI, ADIP Management Committee, WHO SAGE, etc.) in order to provide timely information regarding the efficacy of Rotarix.

The interim analysis will be based on all subjects from the total vaccinated cohort with follow-up 15 days after dose 3. Only severe wild-type RV GE's with onset beyond 15 days after dose 3 but before visit 6 at 1 year of age (severity=Vesikari score ≥11) will be included.

A blinded review of the database dated 15 Jan 2008 indicates that the interim analysis will include 35 subjects with severe wild-type RV GE. Based on the contribution of these cohorts in the study (70% of the total enrolled cohort), it is anticipated that the final ATP cohort analysis will include a total of 50 subjects with severe wild-type RV GE.

Note that considering the similar efficacy observed in previous efficacy studies and the distribution of GE type observed so far in this study, it is not expected that the VE will differ significantly according to the country (e.g. we do not expect to see 70% efficacy from South Africa versus 30% from Malawi).

The timings for the interim and final analyses are

- Interim: Mid March, 2008
- Final Year 1 follow-up: November 2008
- Final Year 2 follow-up: July 2009

7.2. Procedures for ensuring scientific integrity of the study conclusion

In order to ensure that the risk of erroneous recommendation is controlled and that the scientific integrity of the study is maintained,

1. An OBrien & Fleming alpha spending function will be used at the interim and the final analysis. Therefore based on the anticipated 35 and 50 cases at the interim and final analysis, a 2-sided 1.55% nominal type I will be used at the interim analysis. The 2-sided nominal type I at the final analysis should be 4.51% if the total number of cases is 50. It will be revised according to the actual number of cases at the final analysis.

2. The interim analysis will be conducted by an independent analysis center. Results will be disseminated to GSK & PATH only if they meet prespecified criteria, determined jointly by GSK & PATH. These criteria were based on the degree of confidence in the data, whether positive or negative, that would justify early sharing of data for decision-making.

7.3. Possible outcomes of the interim analysis

The possible outcomes of the interim analysis will be as follows:

- Case 1: Nominal 2 sided P-value < 1.55% ie lower limit (LL) of 2-sided 98.45% CI is above 0%: the interim analysis will have demonstrated statistically significant effect in South Africa (type I error=2.5%). In this case the results will be disseminated within GSK & to PATH. Note that this criterion corresponds to observing a VE above 58%.

Table 1

# of cases in placebo	Total # of cases	observed VE	98.45% CI	
			LL	UL
25	35	80.00%	49.53%	93.01%
24	35	77.08%	43.18%	91.65%
23	35	73.91%	36.17%	90.18%
22	35	70.45%	28.38%	88.57%
21	35	66.67%	19.67%	86.83%
20	35	62.50%	9.86%	84.92%
19	35	57.89%	-1.26%	82.84%
18	35	52.78%	-13.97%	80.56%

The power to meet this criterion and to conclude that VE is > 0% at the final analysis is shown below for different true VE:

Table 2

true VE	Power at interim	Power at final
90%	99.8%	99.8%
80%	97.7%	99.9%
75%	91.3%	99.8%
70%	79.8%	98.7%
65%	64.9%	95.5%
60%	49.5%	88.9%
55%	35.9%	78.9%
50%	25.0%	66.6%
45%	16.9%	53.6%

40%	11.1%	41.4%

- Case 2: Upper limit of 2-sided 95% CI is below 59% ie an observed VE <15%. The probability that this happens and the probability, would this happen, to conclude VE > 0% at the final analysis is shown below:

Table 3

True VE	Probability to get case 2 at the interim	Probability to get a LL for the 2 sided 96.49% CI for VE above 0% with 50 cases at final analysis if case 2 is met at interim
90%	0.00%	91.02%
80%	0.00%	56.48%
75%	0.00%	40.41%
70%	0.00%	28.01%
65%	0.10%	19.10%
60%	0.34%	12.93%
55%	0.92%	8.74%
50%	2.05%	5.92%
45%	3.89%	4.03%
40%	6.58%	2.77%

In this case, the results will be disseminated within GSK & to PATH as the final analysis will very likely be inconclusive.

- Case 3: In all other cases, the interim results will not be disseminated/shared with GSK or PATH. The power for the final analysis to conclude VE > 0% is shown in table 1 as follows:

true VE	Power at interim	Power at final
90%	99.8%	99.8%
80%	97.7%	99.9%
75%	91.3%	99.8%
70%	79.8%	98.7%
65%	64.9%	95.5%
60%	49.5%	88.9%
55%	35.9%	78.9%
50%	25.0%	66.6%
45%	16.9%	53.6%
40%	11.1%	41.4%

In all cases the study will proceed up to the final analysis including the Malawi cohort and no publication/abstract of the interim results will be released.

GlaxoSmithKline

Study Reporting and Analysis Plan Approval

Title:	A phase III, double-blind, randomised, placebo-controlled, multi-center study to assess the efficacy, safety and immunogenicity of two or three doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine given concomitantly with routine EPI vaccinations in healthy infants.
eTrack study number	Rota-037 (102248) – 037 EXT Y2 (111274)
Scope:	All data pertaining to the above study
Date:	19-September-2008
Co-ordinating author:	[redacted]
Other author(s):	[redacted] [redacted]

Approved by:			
Director, Worldwide Clinical Development, Rota virus 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

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LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According to Protocol
BCG	Bacille Calmette-Guérin
CI	Confidence Interval
CRF	Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EPI	Expanded Program of Immunisation
GE	Gastroenteritis
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HRV	Human Rotavirus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IS	Intussusception
LL	Lower limit
MedDRA	Medical Dictionary for Regulatory Activities
ml	Milliliter
OPV	Oral Poliovirus Vaccine
PCR	Polymerase Chain Reaction
RV	Rotavirus
RVP	Rotavirus Vaccine Program
SAE	Serious Adverse Event
U/ml	Units per milliliter
UL	Upper limit
VE	Vaccine Efficacy

1. LIST OF AMENDMENTS TO THE RAP

Date	Description
29-February-2008	First version
19-September-2008	Amendment 1 : • Section 3.4: Include definition of HIV status & of GE episodes • Section 5.3.2: add a summary table on LRT fatalities • Section 3.7.2: The use of an O'Brien & Fleming adjustment for the type I error for the primary objective was added

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2. INTRODUCTION

This document summarizes the planned statistical analyses (Sections 3 & 4) based on the study features as per ROTA-037 (102248); 037 EXT Y2 (111274) Protocol Administrative Change 2 (30-AUG-2007). The changes in the analyses as compared to the protocol/amendment 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 severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

3.2. Secondary Endpoints

Efficacy endpoints:

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the study vaccine until Visit 6.
- In South Africa, occurrence of severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Occurrence of severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

For subjects in Cohort 2 South Africa and the Cohort in Malawi:

- Occurrence of severe RV GE (score ≥ 11 on a 20-point Vesikari scoring system) caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.
- Occurrence of severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 7, and from Visit 6 to Visit 7.

Safety endpoints:

- For all subjects, occurrence of AEs/SAEs leading to drop-out throughout the entire study period.
- For all subjects, occurrence of SAEs throughout the entire study period.

Immunogenicity Endpoints:

- In a subset of subjects, seroconversion rate and Geometric Mean concentration (GMC) to anti-rotavirus IgA antibody at Visit 4.

- In all subjects, seropositivity rate and GMC to anti-rotavirus IgA antibody at Visit 4.

3.3. Study cohorts to be evaluated

Total vaccinated cohort

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

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

Total vaccinated cohort for interim analysis

The total vaccinated cohort for interim analysis will include all subjects from Cohort 1 and Cohort 2 in South Africa:

- who received their full study vaccination course
- who have follow-up beyond 2 weeks after the last dose of the study vaccination course

According-to-protocol (ATP) cohort for safety

The ATP cohort for safety will include all vaccinated subjects:

- who have received at least one dose 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.
- who have not received a replacement vial, except if the appropriate vaccine was administered in “double-blind replacement”.

ATP cohort for efficacy

The ATP cohort for efficacy will include all subjects from ATP cohort for safety:

- who received their full study vaccination course.
- who have no RV other than vaccine strain in diarrhoeal stool samples collected between the day of Dose 1 is administered and 2 weeks after the last dose of the study vaccination course.
- who have entered into the efficacy surveillance period:

  - have follow-up beyond 2 weeks after the last dose of the study vaccination course for analysis of the first and combined efficacy follow-up periods.
  - have follow-up beyond the end of the first efficacy follow-up period for analysis of the second efficacy follow-up period.
- who are part of cohort 2 from South Africa or Malawi for the combined efficacy follow-up period

ATP cohort for immunogenicity

The ATP cohort for immunogenicity will include all subjects from the ATP cohort for safety:

- 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 reporting and analysis plan defined age-interval),
- who comply with vaccination schedule for HRV vaccine or placebo (outside reporting and analysis plan defined interval),
- who comply with blood sampling schedule (outside reporting and analysis plan defined interval),
- for whom immunogenicity data are available, at post sampling timepoint.
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 4.
- who have no concomitant infection unrelated to the vaccine which may influence the immune response.

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

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 cohort for safety.

The ATP cohort for immunogenicity 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 with post-vaccination immunological results are excluded from the ATP cohort for immunogenicity. In such a case, the total vaccinated cohort analyses evaluate whether exclusion from the ATP cohort have biased the results.

The list of applicable elimination codes for each cohort is povided in a separate document (refer to Section 6).

Cohort	Elimination codes	Eli

		Type
Total vaccinated cohort for interim analysis	1010, 1030, 3010, 3020	IA
ATP cohort for analysis for safety	1010-1070	MA
ATP cohort for analysis for immunogenicity	1010-2500	MA
ATP cohort for analysis of the first efficacy follow-up period	1010-1070 3010-3030	MA
ATP cohort for analysis of the combined efficacy follow-up period	1010-1070 3010-3030 4005	MA
ATP cohort for analysis of the second efficacy follow-up period	1010-1070 3010-3030 4005-4020	MA

3.4. Derived and transformed data

Demography

Following amendment 1 **(24 August 2005)** HIV status was determined by ELISA & PCR in subjects having given informed consent at visit 1 or at visit 4, if the subject had already completed visit 1. HIV testing was also possible following adverse events. These additional testings will not be used to define HIV status as these may be associated to a treatment effect and thereby these may bias analyses in the subset of HIV positive subjects. HIV status will bedefined positive if, following visit 1 & 4 procedures, the subject had a positive PCR. HIV status will be negative if ELISA testing was negative without positive PCR.

Efficacy

GE episodes: two occurrences of GE will be classified as separate episodes if there are 5 or more diarrhoea-free days between the episodes.

A GE episode is considered to be a RV GE, if a stool sample taken during or not later than 7 days after the episode is ELISA positive for RV and if RV other than vaccine strain is identified the stool sample. GE episode without stool sample/result available will not be considered in the analysis as a RV GE episode.

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

- The number of days (not necessarily consecutive days) with looser than normal stool (vomiting) are calculated by counting the number of days with presence (>0) of looser than normal stool (vomiting). Missing value at a specific day is considered as absence of looser than normal stool (vomiting) at that day.
- The maximum looser than normal stool (vomiting) is defined as the maximum value observed from the number of looser than normal stool (vomiting) recorded daily during the GE episode.
- As the treatment is recorded in the eCRF, score associated to the treatment can then be directly derived from the eCRF.

- As the dehydration is recorded in the eCRF, score associated to the treatment can then be directly derived from the eCRF**.**

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

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

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

VE = vaccine efficacy = (1- RR)*100 = (1 – (ARV/ARU))*100

Where:

ARU = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one severe RV GE episode / total number of subjects in the placebo group.

ARV = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one severe RV GE episode / total number of subjects in the HRV vaccine group.

RR = relative risk = ARV/ARU

Immunogenicity

The cut-off value of anti-rotavirus IgA antibody defined by the laboratory before the analysis and is described in Section 5.6.2.4 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 antibodies (i.e. concentration greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.

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

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

Safety

For the analysis of SAE/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.

For a given subject, missing or non-evaluable HIV measurements will not be replaced. Therefore, a safety analysis based on the HIV seropositivity status will exclude subjects with missing or non-evaluable HIV measurements.

3.5. Data presentation description

The following decimal description will be used for the demography, efficacy, safety 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
	GMC ratio	2

3.6. Group description

The following groups will be used for the statistical analyses.

Study	Group order in tables	Group label in tables (8 characters only)
102248/037	1	HRV_2D
	2	HRV_3D
	3	HRV_POOL
	4	Placebo

The study vaccination regimen is summarised:

Group	Visit 1	Visit 2	Visit 3
HRV_2D	Placebo	HRV	HRV
HRV_3D	HRV	HRV	HRV
Placebo	Placebo	Placebo	Placebo

3.7. Final analyses

Final analysis for efficacy, safety and immunogenicity for Cohort 1 and 2 in South Africa and the Cohort in Malawi will be performed when subjects have completed Visit 6 at the end of the first efficacy follow-up period. A study report will be written. Access to the individual treatment decode will be strictly controlled until end of the second efficacy follow-up period.

Analysis of data from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be performed after subjects have completed Visit 7, and will be presented in an annex report.

The investigators will receive the study results after completion of the final statistical analysis of data collected until Visit 6. However, access to the individual treatment decode will be provided to the investigators only after the final analyses of the second efficacy follow-up has been performed.

3.7.1. Analysis of demographics/baseline characteristics

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 will be calculated per group. The racial and gender composition will be presented.

HIV status will be presented. HIV status will be defined in an amendment of the RAP as this will not be used for the interim analysis.

The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo will be calculated per group. The median, mean, range and standard deviation of age in months at Visits 6 and 7 or at last contact if the study visit was not performed will also be calculated per group.

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

The percentages of subjects who received concomitant and intercurrent vaccinations will be tabulated by group.

3.7.2. Analysis of efficacy

Vaccine efficacy will be calculated by HRV group and for pooled HRV groups, with their 95% CI against:

- Severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains of G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains of non-G1 serotype during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Any RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.
- Severe RV GE caused by the circulating wild-type RV strains during the period starting from Dose 1 of the HRV vaccine or placebo until Visit 6.
- In South Africa, severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks post HRV dose 2 or 3) before the beginning of the RV season.
- Severe GE during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6.

In addition, vaccine efficacy will be calculated, with their 95% CI, against

- severe RV GE caused by the circulating wild-type RV strains, hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE, severe RV GE (G1 and non-G1) for the second and combined efficacy periods and for pooled HRV groups.
- severe RV GE caused by the circulating wild-type RV strains after 3 doses of HRV vaccine versus 2 doses of HRV vaccine for the combined efficacy period.

The primary objective will be reached if the 2-sided p-value for the null hypothesis of no vaccine efficacy for the pooled HRV groups against severe RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6 is below the O'Brien & Fleming type I error adjusted for the 35 subjects with severe RV GE included in the interim analysis. This

adjustement will be obtained from EAST using the total number of subjects with severe RV GE at the final analysis (ATP cohort for efficacy)

Additional supportive and exploratory analyses will be performed (i.e. efficacy against GE requiring hospitalisation, efficacy from Dose 1 until 2 weeks after Dose 3 of study vaccination, time to events analysis, efficacy against severe RV GE using alternative scoring systems other than the Vesikari system).

3.7.3. Analysis of safety

The percentage of subjects with SAEs reported during the study period will be tabulated by group according to Medical Dictionary for Regulatory Activities (MedDRA) classification, with its exact 95% CI.

The percentage of subjects with SAEs coded to the various MedDRA preferred terms (PT) categories for “Pneumonia disease” during the study period will be tabulated by group, with its exact 95% CI. “Pneumonia disease” is defined as all Preferred Terms under the SOC 'Infections and infestations ' that contains the word 'pneumonia.

The percentage of subjects with AEs/SAEs leading to subject drop-out will be tabulated by group according to MedDRA classification, with its exact 95% CI.

Exploratory safety analyses will be performed according to the HIV seropositivity status.

The height and weight increase from Visit 1 to Visits 4, 6 and 7 will be summarised by group.

3.7.4. Analysis of immunogenicity

For each treatment group, at each time point that a given antigen is measured,

- Seropositivity/seroconversion rates and their exact 95% CI will be tabulated.
- GMCs and their 95% CI will be calculated.

The distribution of anti-rotavirus IgA antibody concentrations at Visit 4 will be displayed using reverse cumulative curves.

The asymptotic standardised 95% CI for difference in the percentage of subjects who were seropositive for anti-rotavirus IgA antibody concentrations at Visit 4 between each HRV group and placebo group, and between pooled HRV groups and placebo group will be computed.

3.7.5. Methodology for computing CI

All CI will be 2 sided 95% CI.

- The exact 95% CIs for proportion within a group will be calculated from Proc StatXact 7.0 assuming independence between doses. Proc StatXact 7.0 was also used to derive the standardized asymptotic 95% CI for the group difference in

proportion [ROBERT G. NEWCOMBE , INTERVAL ESTIMATION FOR THE DIFFERENCE BETWEEN INDEPENDENT PROPORTIONS: COMPARISON OF ELEVEN METHODS, Statist. Med. 17, 873-890 (1998): the standardized asymptotic method used within GSK Bio is method 6.

- The 95% CI for GMC 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 concentrations were normally distributed with unknown variance. The 95% CI for the GMC 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

An interim analysis on vaccine efficacy against any RV GE and severe RV GE will be performed on the efficacy data collected from Cohort 1 and Cohort 2 in South Africa until the cut off date of 31 August 2007. The interim analysis will be conducted by the independent data center supporting the IDMC in order to maintain the blind. The interim analysis will be based on the total vaccinated cohort for the subset of subjects with efficacy follow-up 2 weeks beyond study dose 3. The estimated VE against any wild-type RV GE and severe wild-type RV GE will be provided for the pooled HRV groups versus the placebo group. Distribution of RV GE by serotype will also be available although this will not be provided by group. The interim analysis will be disseminated as described in Section 7.

4. CHANGE FROM PROTOCOL

Rules for dissemination of the interim analysis were set (refer to Section 7).

The following efficacy endpoints can not be evaluated as it was not recorded in the eCRF if re-hydration therapy was given in a medical facility except if hospitalization occured

- Occurrence of hospitalisation and/or supervised re-hydration therapy (equivalent to WHO plan B or C) in a medical facility for RV GE caused by the circulating wild-type RV strains during the period from 2 weeks after the last dose of HRV vaccine or placebo until Visit 6/7, and from Visit 6 to Visit 7.

5. ANNEX 1: INDIVIDUAL LISTINGS AND TEMPLATE OF TABLES

5.1. Individual listings for the final analysis up to Visit 6

The following individual data listings will be provided:

Appendix Table II.Cii - Serious Adverse Events reported up to Visit 6 for subjects who died before Visit 6 (unblinded)

Appendix Table II.Ciii - Serious Adverse Events reported up to Visit 6 for subjects who do not died before Visit 6 (blinded)

5.2. Individual listings for the final analysis up to Visit 7

The following individual data listings will be provided:

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.D - General medical history - Physical examination

Appendix Table I.Ei - Conclusion

Appendix Table I.F - Height and weight

Appendix Table I.G - Vaccination procedure

Appendix Table I.H - Reason for non-eligibility

Appendix Table II.Ci - Non-serious Adverse Events leading to drop-out

Appendix Table II.Cii - Serious Adverse Events

Appendix Table II.Di - Concomitant medications

Appendix Table II.Dii - Concomitant vaccinations

Appendix Table III.A – Immunogenicity

Appendix Table IV.A - Gastroenteritis stool collection results

Appendix Table VA – Detailed information of GE episodes

Appendix Table VIA – HIV test by Visit

Appendix Table VIB – Detailed information of HIV tests and results

5.3. List of tables for the final analysis

5.3.1. For Demographics Analysis:

TABLE # in reference of section 5.4	Table Title	Interim analysis	Final Analysis	Macro
Table D 1	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts (safety and immunogenicity) with reasons for exclusion	CR£	CR	%ELIMLIST
Table D 2	Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for Efficacy with reasons for exclusion		CR	%ELIMLIST
Table D 3	Number of subjects by center (Total vaccinated cohort)		ST	%CENTER
Table D 4	Number of subjects enrolled in each country - Total vaccinated cohort		CR	%Freq_dis
Table D 4	Number of subjects enrolled in each country , for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£		%Freq_dis
Table D 5	Number of subjects at each visit and list of withdrawn subjects up to visit 6 (Total vaccinated cohort)		WT	%DROPOUT
Table D 5	Number of subjects at each visit and list of withdrawn subjects up to visit 7 (Total vaccinated cohort)		WT	%DROPOUT
Table D 6	Number of subjects entered, completed and withdrawn with reason for withdrawal at Visit 6 (Total vaccinated cohort)		CR	%DROP_SUM
Table D 6	Number of subjects entered, completed and withdrawn with reason for withdrawal at Visit 7 (Total vaccinated cohort)		CR	%DROP_SUM
Table D 7	Deviations from specifications for age and intervals between study visits (Total Vaccinated Cohort)		ST	%INT_VAL
Table D 7	Deviations from specifications for age and intervals between study visits (ATP cohort for immunogenicity)		WT	%INT_VAL
Table D 8	Number of days between the 3 doses of HRV vaccine/Placebo (Total vaccinated cohort)		ST	%INT_VAL
Table D 9	Minimum and maximum activity dates (Total vaccinated cohort)		WT	%DATE
Table D 10	Summary of demographic characteristics (Total vaccinated cohort)		ST*$	%DEMOGRA
Table D 10	Summary of demographic characteristics, for	CR£		%DEMOGRA

TABLE # in reference of section 5.4	Table Title	Interim analysis	Final Analysis	Macro
	pooled HRV groups and placebo group (Total vaccinated cohort for interim analysis)			
Table D 10	Summary of demographic characteristics (ATP cohort for Immunogenicity)		ST	%DEMOGRA
Table D 10	Summary of demographic characteristics (ATP cohort for efficacy)		CR	%DEMOGRA
Table D 11	Increase in height and weight from Visit 1 to Visits 4, 6 and 7 (Total vaccinated cohort)		ST$	%FREQ_DIS
Table D 12	Summary of co-administered vaccinations by dose – Total vaccinated cohort		ST$	%FREQ_DIS
Table D 13	Summary of vaccinations other than HRV/placebo administered from birth up to Visit 7, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)		ST$	%FREQ_DIS
Table D 14	Summary of HIV tests and results performed during the study (Total vaccinated cohort)		CR$	%FREQ_DIS
Table CTRS 1	Demography of CTRS – Pooled countries		CTRS	%CTR_DEMOG

CR = Within the clinical report
CR£: clinical report generated if allowed (refer to section 7)
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure
CTRS=table for use in the clinical trial registry summary
$=in addition similar tables will be generated for each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
*: 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

5.3.2. For Reactogenicity Analysis:

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 1	Number and percentage of subjects who received HRV/placebo vaccine dose(s) (Total vaccinated cohort)		CR*	%EXPO
Table R 2	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort		ST	%UNSOL
Table R 2	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST/ CTRS	%UNSOL
Table R 3	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 3	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 4	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort		CR	%UNSOL
Table R 4	Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		CR	%UNSOL
Table R 5	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	vaccinated Cohort)			
Table R 5	Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort		ST *$	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST*$	%UNSOL
Table R 6	Percentage of subjects reporting SAEs coded to the various MedDRA Preferred Terms categories for “Pneumonia disease” occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (total vaccinated cohort)		ST	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort		ST*	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST*	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST*$	%UNSOL
Table R 6	Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up		ST*$	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	to Visit 7 - Total vaccinated cohort			
Table R 6	Percentage of subjects reporting SAEs coded to the various MedDRA Preferred Terms categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (total vaccinated cohort)		ST	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST*	%UNSOL
Table R 6	Percentage of HIV positive subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST*	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs coded to the various MedDRA Preferred Terms categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) assessed as related to vaccination occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 7	Statistical comparisons between groups for the percentage of subjects with SAEs coded to the various MedDRA Preferred Terms categories for "Pneumonia disease" occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort		ST *$	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		CR *$	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST *$	%UNSOL
Table R 8	Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		CR *$	%UNSOL
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	(SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort			
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 9	Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) assessed as related to vaccination occurring from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 10	Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visits 6 – Total vaccinated cohort		ST	%UNSOL
Table R 10	Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visits 7 – Total vaccinated cohort		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 11	Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities due to "Pneumonia disease" from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities due to "Pneumonia disease" from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities due to "Pneumonia disease" from occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities associated to the MedDRA high level term "lower respiratory tract and lung infection" from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort		ST	%UNSOL
Table R 11	Percentage of subjects with fatalities fatalities associated to the MedDRA high level term "lower respiratory tract and lung infection" from dose 1 of HRV vaccine or placebo up to Visit 7 - Total vaccinated cohort		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities associated to the MedDRA high level term "lower respiratory tract and lung infection" from occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities from Dose 1 of HRV vaccine or placebo up		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	to Visit 6(Total vaccinated Cohort)			
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities due to "Pneumonia disease" from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 12	Statistical comparisons between groups for the percentage of subjects with fatalities from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated Cohort)		ST	%UNSOL
Table R 13	Listing of fatalities from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 13	Listing of fatalities from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV positive subjects from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV negative subjects from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for subjects with unknown HIV status from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV positive subjects from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for HIV negative subjects from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 14	Summary of fatalities by dose and group for subjects with unknown HIV status from		WT	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
	Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)			
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		WT	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		WT	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV positive subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV negative subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with unknown HIV status fwith fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV positive subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		ST	%UNSOL
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of HIV negative subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		ST	%UNSOL

TABLE # in reference of annex 1	Table Title	Interim Analysis	Final Analysis	Macro
Table R 15	Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with unknown HIV status fwith fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 7 (Total vaccinated cohort)		ST	%UNSOL
Table R 16	Subjects with serious adverse events reported from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)		ST	%SAE
Table R 16	Subjects with serious adverse events reported after Visit 6 up to Visit 7 (Total vaccinated cohort)		ST	%SAE
Table CTRS 2	Number (%) of subjects with serious adverse events from Dose 1 up to Visit 7(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
$=in addition similar tables will be generated for each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
*: 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.

For the analysis on AEs/SAEs leading to drop-out, the following rules will be applied

Rule 1 : In case of withdrawal of the subject because of death, only SAEs reported in the CIOMS of the SAEs leading to death will be included in the analysis. In other situations, only SAEs reported in the last CIOMS before withdrawal of the subject will be included in the analysis of SAEs leading to drop-out.

Rule 2: Non-SAEs and SAEs with missing or incomplete start date will be kept in the analysis of non-SAEs and SAEs leading to drop-out

5.3.3. For Immunogenicity Analysis:

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis	Macro
Table I 1	Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity)		CR*$/CTRS	%GMT
Table I 1	Anti-rotavirus IgA antibody GMC and seropositivity rates for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Table I 2	Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)		CR*$/CTRS	%GMT
Table I 2	Anti-rotavirus IgA antibody GMC and seroconversion rates for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity)		CR*$	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity)		CR*$	%GMT
Table I 3	Anti-rotavirus IgA antibody GMC calculated on subjects who seroconverted for anti-rotavirus IgA antibodies for HIV positive subjects (ATP cohort for immunogenicity)		ST	%GMT
Figure I 1	Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at visit 4 (ATP cohort for immunogenicity)		ST	%REVCUM ps:logscale=10
Table I 4	Difference between groups in percentage of subjects seropositive for anti-rotavirus IgA antibody at Visit 4 - ATP cohort for immunogenicity		CR	%SP_CI
Table I 5	Ratio of anti-rotavirus IgA antibody GMCs at Visit 4 between HRV groups - ATP cohort for immunogenicity		CR	%BIOGMT

CR = Within the clinical report
ST = As a supplementary table or figure
WT = As a working or CTRS table or figure
$=in addition similar tables will be generated for each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
*: a complementary analysis based on the Total Vaccinated cohort will be provided if more than 5% of the vaccinated subjects are excluded from that cohort. The resulting tables will appear as supplemental tables.

5.3.4. For Efficacy Analysis

The tables and graphs below will also be done for the period from 2 weeks after dose 3 until Visit 7, for the ATP cohort for efficacy - combined efficacy follow-up period.

The tables and graphs below will also be done for the period from Visit 6 up to Visit 7, for the ATP cohort for efficacy - second efficacy period.

The tables and graphs below will also be done for the period from Dose 1 up to Visit 6, for the Total vaccinated cohort.

The tables and graphs below will also be done for the period from Dose 1 up to Visit 7, for the Total vaccinated cohort. Cox method will be used for the computation of vaccine efficacy.

Only GE episodes in which wild-type RV (i.e. other than the vaccine strain) is identified in a stool specimen will be included in the efficacy analysis, except for Table E1.

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
Table E 1	Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from dose 1 up to Visit 6- 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 3 up to Visit 6 - ATP cohort for efficacy		CR*
Table E 2	Percentage of HIV positive subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 3	Percentage of GE episodes with no available stool results from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST*
Table E 3	Percentage of GE episodes with no available stool results from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£	
Table E 4	Percentage of GE episodes with missing information for the number of looser than normal stools per day during the GE episode from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST
Table E 5	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 by severity using the 20-point Vesikari scale - ATP cohort for efficacy		CR*
Table E 5	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 by severity using the 20-point Vesikari scale for HIV positive subjects - ATP cohort for efficacy		ST
Table E 6	Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by severity using the 24-point Clark scale - ATP cohort for efficacy		ST
Table E 7	Percentage of subjects with RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*
Table E 8	Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*
Table E 9	Percentage of subjects who were fully vaccinated (at least 2 weeks after Dose 3) before the beginning of the RV season In South Africa - ATP cohort for efficacy		ST
Table E 10	Number of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*$
Table E 10	Number of RV GE episodes reported from 2 weeks after	CR£	

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
	Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, by G serotype and P genotype and for pooled groups - Total vaccinated cohort for interim analysis		
Table E 11	Number of severe RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy		ST*$
Table E 12	Characteristics (based on Vesikari scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy		ST
Table E 12	Characteristics (based on Vesikari scale) of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 13	Characteristics (based on Clark scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy		ST
Table E 13	Characteristics (based on Clark scale) of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 14	Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST*$
Table E 14	Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£	
Table E 15	Percentage of subjects reporting RV GE and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		CR *$/CTRS
Table E 15	Percentage of subjects reporting RV GE and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis	CR£	
Table E 16	Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - ATP cohort for efficacy		ST
Table E 17	Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		CR *$/CTRS
Table E 17	Percentage of subjects with severe RV GE episodes and efficacy during the period from 2 weeks after Dose 3 up to Visit 6 for the subset of subjects who were fully vaccinated (at least 2 weeks after Dose 3) before the beginning of the RV season In South Africa - ATP cohort for efficacy		ST/CTRS
Table E 17	Percentage of subjects with severe RV GE episodes and efficacy during the period from 2 weeks after Dose 3 up to Visit 6 for the subset of subjects who were fully vaccinated		ST

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
	(at least 2 weeks after Dose 3) after the beginning of the RV season In South Africa - ATP cohort for efficacy		
Table E 17	Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 or 31 August 2007 whichever is the earliest, for pooled HRV groups and placebo group - Total vaccinated cohort for interim analysis efficacy	CR£	
Table E 18	Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - ATP cohort for efficacy		ST/CTRS
Table E 19	Percentage of subjects reporting RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 20	Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST$
Table E 21	Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - ATP cohort for efficacy		ST
Table E 22	Percentage of subjects reporting RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 23	Percentage of subjects reporting all cause GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST$
Table E 23	Percentage of subjects reporting all cause severe GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		CR$/CTRS
Table E 24	Percentage of subjects hospitalized and/or treated with re-hydration therapy due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST/CTRS
Table E 24	Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 - ATP cohort for efficacy		CR
Table E 25	Percentage of subjects hospitalized and/or treated with re-hydration therapy due to GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy		ST
Table E 25	Percentage of subjects hospitalized due to GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 - ATP cohort for efficacy		ST

TABLE #	Abbreviated Title	Interim Analysis	Final Analysis
Table E 26	Percentage of subjects reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by status of anti-rotavirus IgA antibody concentration after Dose 3 - ATP cohort for efficacy		ST
Table E 26	Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by status of anti-rotavirus IgA antibody concentration after Dose 3 - ATP cohort for efficacy		ST
Table E 27	Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by Cox - ATP cohort for efficacy		ST
Figure E 1	Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 2	Distribution of Clark score for RV GE reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 3	Seasonal distribution of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy		ST$
Figure E 4	Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy		ST$
Figure E 5	Efficacy of the vaccine against RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 6	Efficacy of the vaccine against RV GE episodes with a score ≥X on the Clark scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy		ST
Figure E 7	The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST
Figure E 7	The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST
Figure E 7	The Kaplan Meier curve for severe RV GE due to non-G1 serotypes from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy		ST

CR = Within the clinical report
CR£: clinical report generated if allowed (refer to section 7)
ST = As a supplementary table or figure
WT = As a working table or figure
$ = In addition similar tables will be generated by each country and for cohort 1 and 2 in South Africa. The resulting tables will appear as supplemental tables.
* = In addition similar tables will be generated for the analysis from dose 1 of HRV/placebo up to 14 post dose 3 of HRV/placebo and from dose 1 of HRV/placebo up to before dose 3 of HRV/placebo on the total vaccinated cohort

5.4. Template of tables

Table D 1 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts (safety and immunogenicity) with reasons for exclusion

	Total			HRV_2D		HRV_3D		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Number of vaccines prepared									
Subjects or vaccine number not allocated (code 1010)									
Total enrolled cohort									
Total vaccinated cohort									
Randomisation code broken at the investigator site (code 1060)									
Study vaccine dose not administered according to protocol (code 1070)									
ATP cohort for safety									
Protocol violation (inclusion/exclusion criteria) (code 2010)									
Administration of any medication forbidden by the protocol (code 2040)									
Underlying medical condition forbidden by the protocol (code 2050)									
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)									
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)									
Essential serological data missing (code 2100)									
Subjects with incomplete vaccination schedule but with post serological result (code 2500)									
ATP cohort for immunogenicity									

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
Data source = Appendix table IA

Table D 2 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohorts for Efficacy with reasons for exclusion

	Total			HRV_2D		HRV_3D		Placebo	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Number of vaccines prepared									
Subjects or vaccine number not allocated (code 1010)									
Total enrolled cohort									
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 efficacy follow-up period(code 3020)									
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 3 which may influence efficacy response (code 3030)									
ATP cohort for efficacy - first period (Code 4005) Subjects not planned in the protocol to be part of the second efficacy follow-up period **ATP cohort for efficacy - combined period** (Code 4020) Subjects not entered into the surveillance period of the second efficacy follow-up period **ATP cohort for efficacy - 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 cohort for efficacy for the first efficacy follow-up period include all vaccinated subjects with no elimination codes beginning with one thousand or three thousand. The ATP cohort for efficacy for combined efficacy follow-up periods include all vaccinated subjects with no elimination codes beginning with one thousand or three thousand or with elimination code 4005. The ATP cohort for efficacy for the second efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one thousand, three thousand or four thousand.
Data source = Appendix table IA

Table D 3 Number of subjects by center (Total vaccinated cohort)

	HRV_2D	HRV_3D	Placebo	Total	
Center	**n**	**n**	**n**	**n**	**%**
All					

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 x 100
Center = GSK Biologicals assigned center number
Data source = Appendix table IB

Table D 4 Number of subjects enrolled in each country - Total vaccinated cohort

	HRV_2D	HRV_3D	Placebo	Total	
Country	**n**	**n**	**n**	**n**	**%**
South Africa (cohort 1)	XXX	XXX	XXX	XXX	XX.x
South Africa (cohort 2)					
Malawi					

N = number of subjects enrolled in the considered group or in total (sum of both groups)
n/% = number/ percentage of subjects enrolled in each group or in total for a given country.
Data source = Appendix table IB

Table D 5 Number of subjects at each visit and list of withdrawn subjects up to visit 6 (Total vaccinated cohort)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
HRV_2D	VISIT1	Xxx		
			no. xxx	MIGRATION FROM STUDY AREA
			no. xxx	MIGRATION FROM STUDY AREA
	VISIT2	Xxx		
			no. xxx	CONSENT WITHDRAWAL
			no. xxx	MIGRATION FROM STUDY AREA
			no. xxx	MIGRATION FROM STUDY AREA
			no. xxx	MIGRATION FROM STUDY AREA
	VISIT3	Xxx		
			no. xxx	MIGRATION FROM STUDY AREA
	VISIT4	Xxx		
			no. xxx	Xxx
	VISIT5	Xxx		
			no. xxx	Xxx
	VISIT6	Xxx		
			no. xxx	Xxx
HRV_3D	VISIT1	Xxx		
			no. xxx	Xxx
	VISIT2	Xxx		
			no. xxx	Xxx
	VISIT3	Xxx		
			no. xxx	Xxx
	VISIT4	Xxx		
			no. xxx	Xxx
	VISIT5	Xxx		
			no. xxx	Xxx
	VISIT6	Xxx		
			no. xxx	Xxx
Pacebo	VISIT1	Xxx		
			no. xxx	Xxx
	VISIT2	Xxx		
			no. xxx	Xxx
	VISIT3	Xxx		
			no. xxx	Xxx
	VISIT4	Xxx		
			no. xxx	Xxx
	VISIT5	Xxx		
			no. xxx	Xxx
	VISIT6	Xxx		
			no. xxx	Xxx

Data source = Appendix table ICi, Appendix table IEi

Table D 6 Number of subjects entered, completed and withdrawn with reason for withdrawal at Visit 6 (Total vaccinated cohort)

	Group			
	HRV_2D	**HRV_3D**	**Placebo**	**Total**
Number of subjects vaccinated	1600	1600	1600	4800
Number of subjects completed	Xxx	Xxx	Xxx	Xxx
Number of subjects withdrawn	Xxx	Xxx	Xxx	Xxx
Reasons for withdrawal :				
Serious Adverse Event	Xxx	Xxx	Xxx	Xxx
Non-serious adverse event	Xxx	Xxx	Xxx	Xxx
Protocol violation	Xxx	Xxx	Xxx	Xxx
Consent withdrawal (not due to an adverse event)	Xxx	Xxx	Xxx	Xxx
Migrated/moved from study area	Xxx	Xxx	Xxx	Xxx
Lost to follow-up (subjects with incomplete vaccination course)	Xxx	Xxx	Xxx	Xxx
Lost to follow-up (subjects with complete vaccination course)	Xxx	Xxx	Xxx	Xxx
Others	xxx	Xxx	Xxx	Xxx

Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed visit 6
Withdrawn = number of subjects who did not come for the visit 6
Data source = Appendix table IEi

Table D 7 Deviations from specifications for age and intervals between study visits (Total Vaccinated Cohort)

		Age at Dose 1 of HRV/placebo	**Dose 1 of HRV/placebo – Dose 2 of HRV/placebo**		**Dose 2 of HRV/placebo – Dose 3 of HRV/placebo**		**Dose 3 of HRV/placebo – BL at Visit 4**	
GROUP		**Protocol**	**Protocol**	**Adapted**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
		from 35 to 76 days	from 28 to 48 days	from 21 to 48 days	from 28 to 48 days	from 21 to 48 days	from 30 to 48 days	from 21 to 48 days
HRV_2D	**N**	1890	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	n	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	%	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	range	X to x	X to x	X to x	X to x	X to x	X to x	X to x
HRV_3D	**N**	1890	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	n	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	%	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	range	X to x	X to x	X to x	X to x	X to x	X to x	X to x
Placebo	**N**	1890	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	n	Xxx	Xxx	Xxx	xxx	xxx	xxx	xxx
	%	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	range	X to x	X to x	X to x	X to x	X to x	X to x	X to x

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
BL= blood sample
Data source = Appendix table IB, Appendix table ICi

Table D 8 Number of days between the 3 doses of HRV vaccine/Placebo (Total vaccinated cohort)

	HRV_2D	HRV_3D	Placebo	Total
Number of days between Dose 1 and Dose 2 of HRV vaccine/placebo				
N	XXX			
Mean	XX.x			
SD	XX.xx			
Minimum	XX			
Q1	XX.x			
Median	XX.x			
Q3	XX.x			
Maximum	XX			
Number of days between Dose 2 and Dose 3 of HRV vaccine/placebo				
N	XXX			
Mean	XX.x			
SD	XX.xx			
Minimum	XX			
Q1	XX.x			
Median	XX.x			
Q3	XX.x			
Maximum	XX			

N for number of days between Dose 1 and Dose 2: N= Number of subjects with dose 1 and dose 2 administered
N for number of days between Dose 2 and Dose 3: N= Number of subjects with dose 2 and dose 3 administered
Q1 = 25th percentile
Q3 = 75th percentile
SD = standard deviation
Data source= Appendix Table ICi

Table D 9 Minimum and maximum activity dates (Total vaccinated cohort)

Activity number	Visit Number	Minimum date	Maximum date

Table D 10 Summary of demographic characteristics (Total vaccinated cohort)

Characteristics	Parameters or Categories	HRV_2D N=		HRV_3D N=		Placebo N=		Total N=	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (Weeks) at Dose 1 of HRV vaccine/placebo	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (Weeks) at Dose 2 of HRV vaccine/placebo	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (Weeks) at Dose 3 of HRV vaccine/placebo	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (months) at Visit 6 or at last Contact if visit 6 not performed	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Age (months) at Visit 7 or at last Contact if visit 7 not performed	Mean		-		-		-		-
	SD		-		-		-		-
	Median		-		-		-		-
	Minimum		-		-		-		-
	Maximum		-		-		-		-
Gender	Female								
	Male								
Race	African heritage / African american								
	American Indian or Alaska Native								
	Asian – Central/South Asian heritage								
	Asian – East Asian heritage								
	Asian – Japanese heritage								
	Asian – South East Asian heritage								
	Native Hawaiian or Other Pacific Islander								
	White – Arabic / North African heritage								
	White – Caucasian / European heritage								
	Other								
Height at visit 1 (cm)	Mean								
	Sd								
	Median								
Weight at visit 1 (kg)	Mean								
	Sd								
	Median								
BMI at visit 1	Mean								

(kg/m²)	**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 (Weeks) = age expressed in weeks
Data source = Appendix table IB

Table D 11 Increase in height and weight from Visit 1 to Visits 4, 6 and 7 (Total vaccinated cohort)

Visit	Characteristics	Parameters or Categories	HRV_2D N=	HRV_3D N=	Placebo N=	Total N=
			Value	Value	Value	Value
Visit 4	Increase in height (cm) from Visit 1	Mean	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
	Increase in weight (kg) from Visit 1	Mean	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
Visit 6	Increase in height (cm) from Visit 1	Mean	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
	Increase in weight (kg) from Visit 1	Mean	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
Visit 7	Increase in height (cm) from Visit 1	Mean	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx
	Increase in weight (kg) from Visit 1	Mean	Xxx	Xxx	Xxx	Xxx
		SD	Xxx	Xxx	Xxx	Xxx
		Median	Xxx	Xxx	Xxx	Xxx
		Unknown	Xxx	Xxx	Xxx	Xxx

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Data source = Appendix table IB

Table D 12 Summary of co-administered vaccinations by dose – Total vaccinated cohort

Category	HRV_2D N=		HRV_3D N=		Placebo N=		Total N=	
	n	%	n	%	n	%	n	%
Dose1								
Any								
BCG								
DTPw-HB								
HIB								
OPV								
Dose 2								
	HRV_2D		HRV_3D		Placebo		Total	
	N=		N=		N=		N=	
	n	%	n	%	n	%	n	%
Any								
BCG								
DTPw-HB								
HIB								
OPV								
Dose 3								
	HRV_2D		HRV_3D		Placebo		Total	
	N=		N=		N=		N=	
	n	%	n	%	n	%	n	%
Any								
BCG								
DTPw-HB								
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
Data source = Appendix table I.Ci and II.Dii

Table D 13 Summary of vaccinations other than HRV/placebo administered from birth up to Visit 7, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)

Before Dose 1												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 1 and Dose 2§												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 2 and Dose 3*												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 3 and Visit 6µ												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Between Dose 3 and Visit 7£												
	HRV_2D (N=xx)			**HRV_3D (N=xx)**			**Placebo N=xxx**			**Total N=xxx**		
Characteristics	**#**	**n**	**%**	**#**	**n**	**%**	**#**	**N**	**%**	**#**	**N**	**%**
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
DTPw-HB	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

N = Before Dose 1: total number of subjects having received dose 1 of HRV/placebo
Between Dose 1 and dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and dose 3: total number of subjects having received dose 2 of HRV/placebo
Between Dose 3 and Visit 6: total number of subjects having received dose 3 of HRV/placebo
Between Dose 3 and Visit 7: total number of subjects having received dose 3 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 dose 3 of HRV/placebo was not administered

µ= up to last contact if Visit 6 was not done

£= up to last contact if Visit 7 was not done

Data source= Appendix table I.Ci and II.Dii

Table D 14 Summary of HIV tests and results performed during the study (Total vaccinated cohort)

HIV status during the study	HRV_2D		HRV_3D		Placebo		Total	
	N=		N=		N=		N=	
	n	%	n	%	n	%	n	%
HIV Test								
	N'=		N'=		N'=		N'=	
	n'	%	n'	%	n'	%	n'	%
Positive Negative Unknown								

N = total number of subjects
n/% = number / percentage of subjects tested for HIV
N' = total number of subjects tested for HIV
n'/% = number / percentage of subjects in a given category

Table R 1 Number and percentage of subjects who received HRV/placebo vaccine dose(s) (Total vaccinated cohort)

Total number Of doses received	HRV_2D (N = XXX)		HRV_3D (N = XXX)		Placebo (N = XXX)		Total (N = XXX)	
	n	%	n	%	n	%	n	%
0	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
1	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
2	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
3	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Any	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

N = number of subjects in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses in each group or in total
Any = number and percentage of subjects receiving at least one dose
Appendix Table I.C.

Table R 2 Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort

	HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 3 Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

	Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo)			
		95% CI				**95% CI**				**95% CI**		
Primary System Organ Class (CODE)	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*												

At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA SOC
%= percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 4 Percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 - Total Vaccinated Cohort

		HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	Preferred term (CODE)	n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
At least one symptom *(each SOC)*	*(each Preferred term)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA Preferred Term
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 5 Statistical comparisons between groups for the percentage of subjects with AEs/SAEs leading to drop out classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

		Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo			
			95% CI				95% CI				95% CI		
Primary System Organ Class (CODE)	Preferred term (CODE)	%	LL	UL	P-value	%	LL	UL	P-value	%	LL	UL	P-value
At least one symptom *(each SOC)*	*(each Preferred term)*												

At least one symptom = number of subjects reporting at least one AEs/SAEs leading to drop-out, whatever the MedDRA Preferred Term
%= percentage of subjects reporting at least once the specified AEs/SAEs leading to drop-out
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified AEs/SAEs leading to drop-out after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 6 Percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort

	HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
			LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified SAE
At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA SOC
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 7 Statistical comparisons between groups for the percentage of subjects with SAEs classified by MedDRA system organ class (SOC) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

	Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo)			
		95% CI				95% CI				95% CI		
Primary System Organ Class (CODE)	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*												

At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA SOC
%= percentage of subjects reporting at least once the specified SAE
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified SAE after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 8 Percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to visit 6 - Total vaccinated cohort

		HRV_2D N=				HRV_3D N=				Placebo N=			
Primary System Organ Class (CODE)	**Preferred term (CODE)**	**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
At least one symptom *(each SOC)*	*(each Preferred term)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting at least once the specified SAE
At least one symptom = number of subjects reporting at least one the specified SAE, whatever the MedDRA Preferred Term
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 9 Statistical comparisons between groups for the percentage of subjects with SAE classified by MedDRA system organ class (SOC) and preferred terms (PT) occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

		Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo			
			95% CI				**95% CI**				**95% CI**		
Primary System Organ Class (CODE)	**Preferred term (CODE)**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
At least one symptom *(each SOC)*	*(each Preferred term)*												

At least one symptom = number of subjects reporting at least one SAE, whatever the MedDRA Preferred Term
%= percentage of subjects reporting at least once the specified SAEs
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified SAE after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 10 Summary of subjects with IS occurring from Dose 1 of HRV vaccine or placebo up to Visits 6 – Total vaccinated cohort

PID	Date of birth	Country	IS type (suspected/probable/possible)	Gender	Age at dose 1 (weeks)	Age at dose 2 (weeks)	Age at dose 3 (weeks)	Age at the start day of the symptom	Previous Dose	Onset day (start date of the symptom)

Table R 11 Percentage of subjects with fatalities classified by MedDRA system organ class (SOC) and preferred term (PT) occurring from dose 1 of HRV vaccine or placebo up to Visit 6 - Total vaccinated cohort

		HRV_2D N =				HRV_3D N =				Placebo N =			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
At least one symptom													
(each SOC)	*(each Preferred term)*												

N=number of subjects in the considered cohort
n/%= number/percentage of subjects reporting the fatal specified symptom
At least one symptom = number of subjects who died during the specified period, whatever the MedDRA Preferred Term
95% CI = exact 95% confidence interval, LL = lower limit, UL = upper limit
Source: Appendix II.Ci

Table R 12 Statistical comparisons between groups for the percentage of subjects with fatalities due to "Pneumonia disease" from occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated Cohort)

	Difference in percentage (HRV_2D minus Placebo)				Difference in percentage (HRV_3D minus Placebo)				Difference in percentage (HRV_POOL minus Placebo			
		95% CI				95% CI				95% CI		
Primary System Organ Class (CODE)	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**	**%**	**LL**	**UL**	**P-value**
Pneumonia disease												

%= percentage of subjects reporting at least one "Pneumonia Disease" related to death
95% CI = asymptotic standardised 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = results of comparison of percentage of subjects reporting the specified "Pneumonia Disease" related to death after any doses between groups by two-sided asymptotic score test for the null hypothesis of identical incidence in both groups
(P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 13 Listing of fatalities from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

Group	dose	Day since last dose	Pid	Case Id	Sex	HIV	Day since dose 1	date of death	Age at death (days)	full treatment	Verbatim

Table R 14 Summary of fatalities by dose and group from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

Dose	Group	number of fatalities

Table R 15 Relative risk stratified by dose between pooled HRV group and placebo group for percentage of subjects with fatalities occurring from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

HRV_POOL over Placebo			
	95% CI		
RR	LL	UL	P-value

RR= relative risk
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
P-value = two-sided exact p_value adjusted for the dose effect for the null hypothesis that the relative risk equals one (P-value less than 0.05 will be used as an aid to highlight potential difference worth further attention. However care must be taken when interpreting putative statistically significant findings since there is no multiplicity adjustment and clinical significance must be taken into account)
Source: Appendix II.Ci

Table R 16 Subjects with serious adverse events reported from Dose 1 of HRV vaccine or placebo up to Visit 6 (Total vaccinated cohort)

Pid	Case Id	Age (Week)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome

MA = medical attention
HO = hospitalization
Dose = Dose given prior to the start of the SAE
Day of onset = Number of days since last vaccine dose
Data source = Appendix table IIC

Table I 1 Anti-rotavirus IgA antibody GMC and seropositivity rates (ATP cohort for immunogenicity)

Group	Timing	N	>= 20 U/ML				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_2D	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	PRE	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

GMC = geometric mean antibody concentration calculated on all subjects
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
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Individual subjects data can be found in Appendix IIIA

Table I 2 Anti-rotavirus IgA antibody GMC and seroconversion rates (ATP cohort for immunogenicity)

Group	Timing	N	>= 20 U/ML				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_2D	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	PIII(M3)	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx

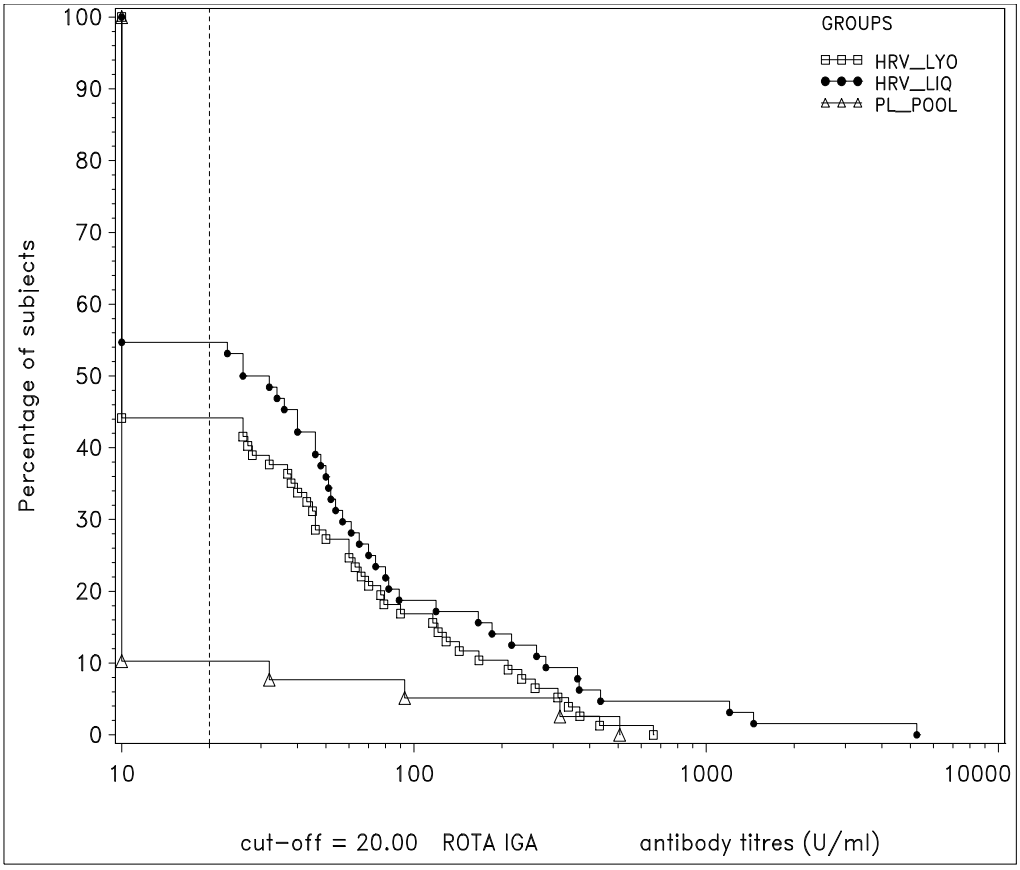
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results at pre and post timepoints
n/% = number/percentage of subjects who seroconverted
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Individual subjects data can be found in Appendix IIIA

Table I 3 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity)

Group	Timing	N	GMC		
			Value	95% CI	
				LL	UL
HRV_2D	PRE	Xxx	Xxx	Xxx	Xxx
	PIII(M3)				
HRV_3D	PRE	Xxx	Xxx	Xxx	Xxx
	PIII(M3)				
HRV_POOL	PRE	Xxx	Xxx	Xxx	Xxx
	PIII(M3)				
Placebo	PRE				
	PIII(M3)				

GMC = geometric mean antibody concentration calculated on seropositive subjects
N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
PRE = pre-vaccination
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Individual subjects data can be found in Appendix IIIA

Figure I 1 Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at visit 4 (ATP cohort for immunogenicity)



Data Source= Appendix Table III.A

Table I 4 Difference between groups in percentage of subjects seropositive for anti-rotavirus IgA antibody at Visit 4 - ATP cohort for immunogenicity

						Difference in seropositivity rate			
								95 % CI	
Group	N	%	Group	N	%	Difference	%	LL	UL
HRV_2D			Placebo			HRV_2D - Placebo			
HRV_3D			Placebo			HRV_3D - Placebo			
HRV_POOL			Placebo			HRV_POOL - Placebo			
HRV_3D			HRV_2D			HRV_3D - HRV_2D			

N = number of subjects with available results
% = percentage of subjects who were were seropositive
95%CI = asymptotic standardized 95% confidence interval; LL = lower limit; UL = upper limit
PIII (M3) = one month after Dose 3 of HRV/Placebo vaccine (visit 4)
Source: Appendix III.A

Table I 5 Ratio of anti-rotavirus IgA antibody GMCs at Visit 4 between HRV groups - ATP cohort for immunogenicity

						GMC ratio			
								95% CI	
Group	N	GMC	Group	N	GMC	Ratio order	Value	LL	UL
HRV_3D			HRV_2D			HRV_3D / HRV_2D			

N = number of subjects with available results
95% CI LL, UL: 95% lower and upper confidence interval limits (one-way ANOVA model)
L.L. = lower limit, U.L. = upper limit

Table E 1 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from dose 1 up to Visit 6- Total vaccinated cohort

Group	N	n	%	95%CI	
				LL	UL
HRV_2D HRV_3D HRV_POOL Placebo					

N = number of subjects included in each group
n/% = number/percentage of subjects with vaccine virus in at least one stool sample collected in case of GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
Data Source= Appendix Table V.A

Table E 2 Percentage of subjects who reported GE episodes, RV GE episodes, severe GE episodes and severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

Event	Total number of episodes reported	HRV_3D		HRV_2D		HRV_POOL		Placebo	
		n	%	n	%	n	%	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 episode
Data Source = Appendix Table IV.A and V.A

Table E 3 Percentage of GE episodes with no available stool results from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy

Category	HRV_2D		HRV_3D		HRV_POOL		Placebo		Total	
	n	%	n	%	n	%	n	%	n	%
	N'=		N'=		N'=		N'=		N'=	
No stools collected Stools collected but no results available										
No stool results available										

N'= number of GE episodes reported
n/%= number/percentage of GE episodes reported within the specified category
Data Source = Appendix Table V.A

Table E 4 Percentage of GE episodes with missing information for the number of looser than normal stools per day during the GE episode from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy

HRV_2D N'=		HRV_3D N'=		HRV_POOL N'=		Placebo N'=		Total N'=	
n	%	n	%	n	%	n	%	n	%

N'= number of GE episodes reported
n/%= number/percentage of GE episodes reported with a maximum number of looser than normal stool per day during the episodes <3 or missing
Data Source = Appendix Table V.A

Table E 5 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 by severity using the 20-point Vesikari scale - ATP cohort for efficacy

Event	Severity using the 20-point Vesikari scale	HRV_2D		HRV_3D		HRV_POOL		Placebo	
		n	%	n	%	n	%	n	%
GE	Mild (1-6) Moderate (7-10) Severe (≥11) Any								
RV GE	Mild (1-6) Moderate (7-10) Severe (≥11) Any		-						

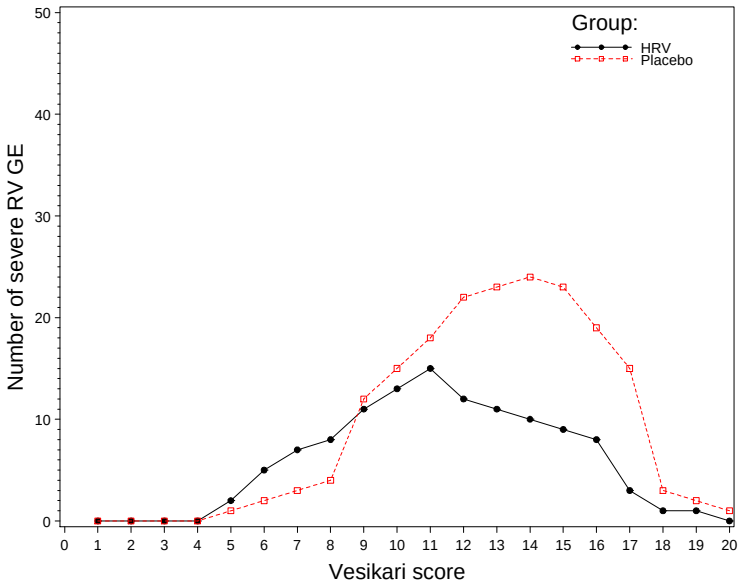
n/% = number/percentage of the specified event reported in each group, by severity using the 20-point Vesikari scale, among all specified events reported during the considered efficacy period
Any = any specified symptom reported, regardless of Vesikari severity scale
Data Source = Appendix Table IV.A and V.A

Table E 6 Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by severity using the 24-point Clark scale - ATP cohort for efficacy

Event	Severity using Clark scale	HRV_2D		HRV_3D		HRV_POOL		Placebo	
		n	%	n	%	n	%	n	%
GE	Mild (1-8)								
	Moderate (9-16)								
	Severe (≥17)								
	Unknown								
	Any								
RV GE	Mild (1-8)								
	Moderate (9-16)								
	Severe (≥17)								
	Any								

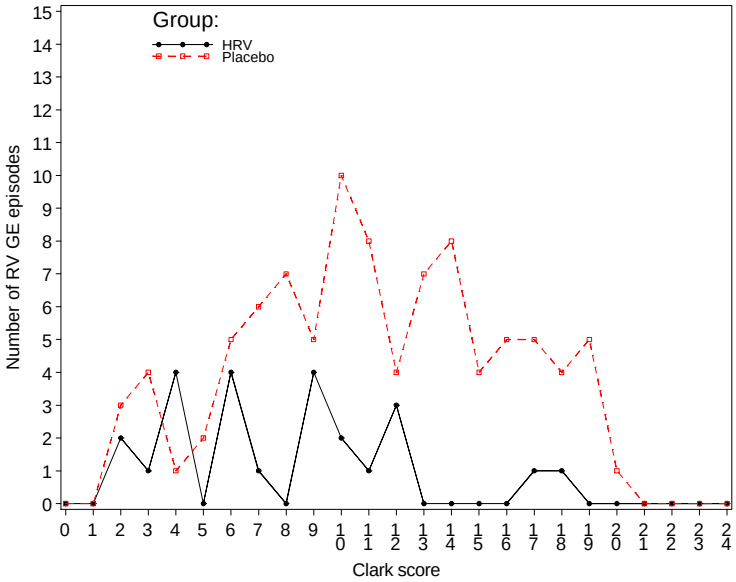
n/% = number/percentage of the specified event reported in each group, by severity using the 24-point Clark scale, among all specified events reported
Any = any specified symptom reported, regardless of Clark severity scale
Data Source = Appendix Table IV.A,and V.A

Figure E 1 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A

Figure E 2 Distribution of Clark score for RV GE reported from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A

Table E 7 Percentage of subjects with RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

	HRV_2D		HRV_3D		HRV_POOL		Placebo	
Serotype	n	%	n	%	n	%	n	%
	N=		N=		N=		N=	
Any								
G1/P8								
G2/P4								
….								

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype
Any = number of subjects reporting at least one RV GE episode, whatever the serotype
Data Source= Appendix Table IVA and V.A

Table E 8 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

	HRV_2D		HRV_3D		HRV_POOL		Placebo	
Serotype	n	%	n	%	n	%	n	%
	N=		N=		N=		N=	
Any								
G1/P8								
G2/P4								
….								

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype
Any = number of subjects reporting at least one severe RV GE episode, whatever the serotype
Data Source= Appendix Table IVA and V.A

Table E 9 Percentage of subjects who were fully vaccinated (at least 2 weeks after Dose 3) before the beginning of the RV season In South Africa - ATP cohort for efficacy

		HRV_2D		HRV_3D		Placebo	
		N=		N=		N=	
Country	Vaccinated before the RV season	n	%	n	%	n	%
South Africa cohort 1	Yes						
	No						
South Africa cohort 2	Yes						
	No						
South Africa	Yes						
	No						

N = number of subjects included in each group
n/%= number/percentage of subjects in the specified category

Table E 10 Number of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV_2D		HRV_3D		HRV_POOL		Placebo	
	n	%	n	%	n	%	n	%
(each country and overall)	N'=		N'=		N'=		N'=	
G1 wild type								
G2								
G4 and G9								
….								

N'= number of RV GE episodes reported
n/%= number/percentage of RV GE episodes reported, by serotype
Data Source= Appendix Table IVA and V.A

Table E 11 Number of severe RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by G serotype and P genotype - ATP cohort for efficacy

Serotype	HRV_2D		HRV_3D		HRV_POOL		Placebo	
	n	%	n	%	n	%	n	%
(each country and overall)	N'=		N'=		N'=		N'=	
G1 wild type								
G2								
G4 and G9								
….								

N'= number of severe RV GE episodes reported
n/%= number/percentage of severe RV GE episodes reported, by serotype
Data Source= Appendix Table IVA and V.A

Table E 12 Characteristics (based on Vesikari scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy

			HRV_2D		HRV_3D		Placebo	
			N'=		N'=		N'=	
Serotype	Characteristics	Parameters or categories	Value or n	%	Value or n	%	Value or n	%
		N'		-		-		-
(Main serotype and overall)	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 looser 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 RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation
Data Source= Appendix Table IVA and V.A

Table E 13 Characteristics (based on Clark scale) of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6, by main serotype and overall - ATP cohort for efficacy

Characteristics	Parameters or Categories	HRV_2D		HRV_3D		HRV_POOL		Placebo	
		N'=		N'=		N'=		N'=	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean SD Median Minimum Maximum								
Duration of looser than normal stools (days)	0 day 1-4 days 5-7 days > 7 days								
Maximum number of looser than normal stools/24 hours	0 2-4 5-7 > 7								
Duration of vomiting (days)	0 - 1 day 2 days 3-5 days > 5 days								
Maximum number of episodes of Vomiting/24 hours	0 1-3 4-6 > 6								
Duration of fever (days)	0 day 1-2 day 3-4 days ≥ 5 days								
Maximum fever reported /24 hours (measured rectally)	< 38.0°C 38.0-38.2°C 38.3-38.7°C ≥ 38.8°C								
Duration of behavioral symptoms	0 day 1-2 days 3-4 days ≥ 5 days								
Behavioral symptoms	Behave as usual Irritable/less playful Lethargic/listless Seizures								

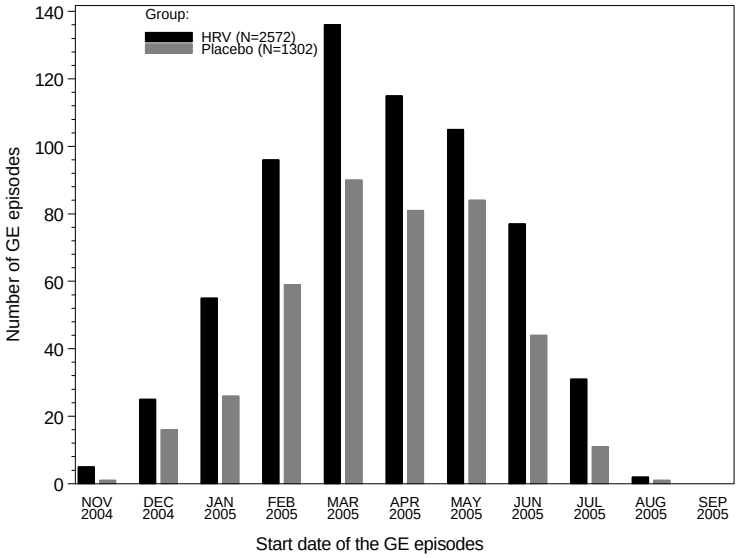
N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation
Data Source= Appendix Table IVA and V.A

Table E 14 Duration (in years) of efficacy follow-up period from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy

Duration (years) of follow-up period	HRV_2D	HRV_3D	HRV_POOL	Placebo
	N=	N=	N=	N=
Total Mean Minimum Q1 Median Q3 Maximum				

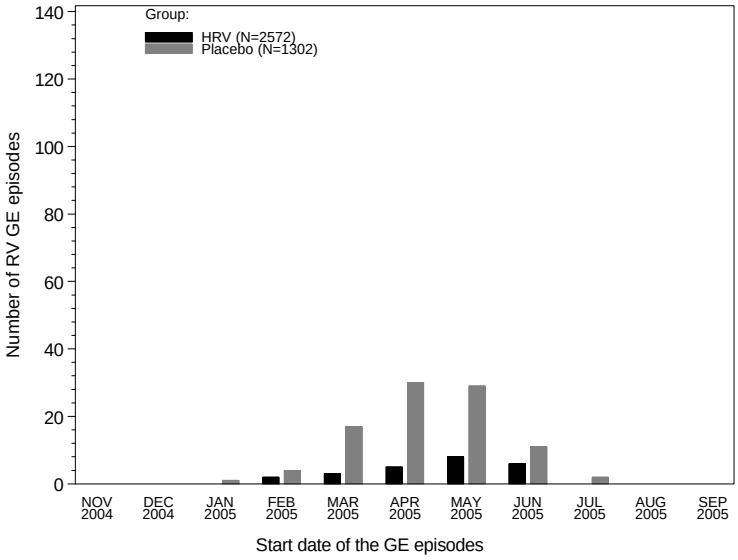
N= Number of subjects included in each group
Total= sum of follow-up period expressed in year
Q1 = 25th percentile
Q3 = 75th percentile
Data Source: Appendix I.Ci

Figure E 3 Seasonal distribution of GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy



N = number of subjects included in each group
Data Source= Appendix Table V.A

Figure E 4 Seasonal distribution of RV GE episodes reported from 2 weeks after Dose 3 up to Visit 6 for pooled HRV groups and placebo group – ATP cohort for efficacy



N = number of subjects included in each group
Data Source= Appendix Table IVA and V.A

Table E 15 Percentage of subjects reporting RV GE and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

	n/N					Vaccine Efficacy			P-Value
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

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
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 16 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - 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_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
G2	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
…….	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
P8	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Pooled Non G1 (G2, …….)	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source = Appendix Table IV.A and V.A

Table E 17 Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 18 Percentage of subjects reporting severe (Vesikari score ≥11) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - 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_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
G2	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
.....	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Pooled Non G1 (G2, ...)	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source = Appendix Table IV.A and V.A

Table E 19 Percentage of subjects reporting RV GE episodes with a score ≥X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

Severity using Vesikari scale	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
≥11	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥12	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥13	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥14	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥15	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥16	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥17	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥18	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥19	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥20	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group

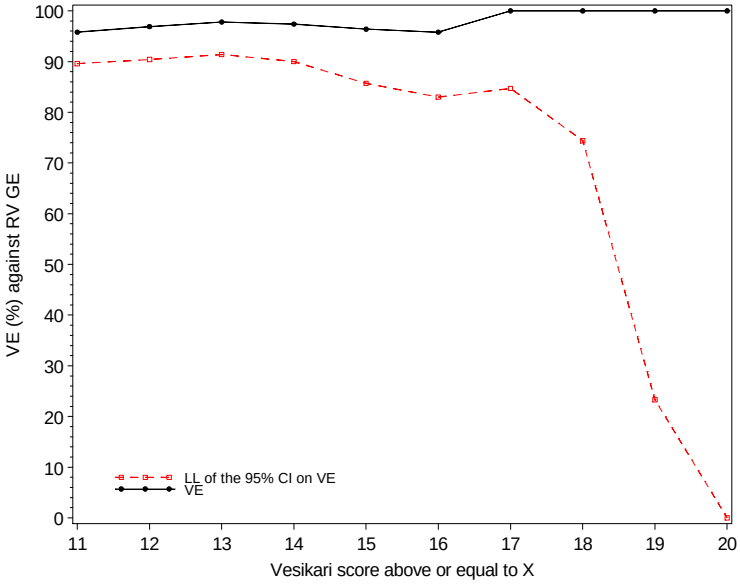
n/% = number/percentage of subjects reporting at least one RV GE episode with a score ≥X on the Vesikari scale, in each group

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

p_value=two-sided exact p_value conditional to the number of episodes

Data Source= Appendix Table IVA and V.A

Figure E 5 Efficacy of the vaccine against RV GE episodes with a score ≥X on the Vesikari scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A
Y-axis has been cut at 0

Table E 20 Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 21 Percentage of subjects reporting severe (Clark score >16) RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by RV serotype - 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_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
G2	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
.....	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Pooled Non G1 (G2, ...)	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode
95% CI=exact 95% Confidence interval; L.L =Lower limit; U.L = upper limit
p_value=two-sided exact p_value conditional to the number of episodes
Data Source = Appendix Table IV.A and V.A

Table E 22 Percentage of subjects reporting RV GE episodes with a score ≥X on the Clark scale and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

Severity using Clark scale	Group	N	n	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
≥17	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥18	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥19	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥20	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥21	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥22	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥23	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
≥24	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group

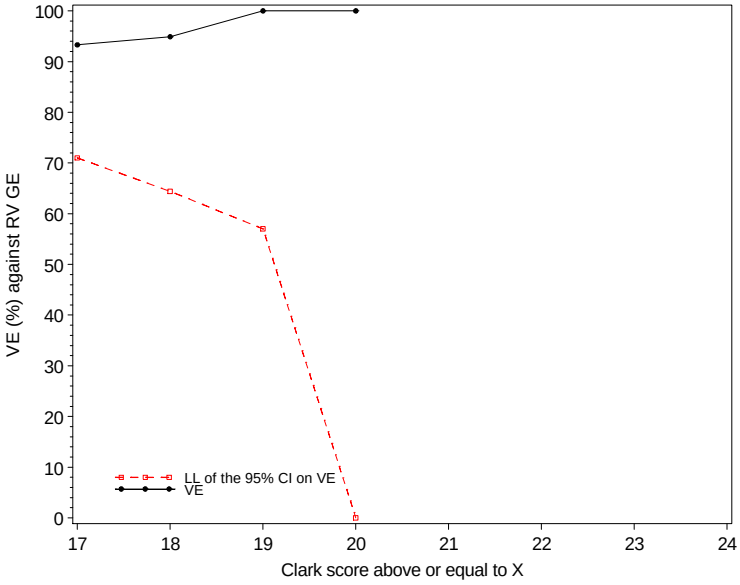
n/% = number/percentage of subjects reporting at least one RV GE episode with a score ≥X on the Clark scale, in each group

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

p_value=two-sided exact p_value conditional to the number of episodes

Data Source= Appendix Table IVA and V.A

Figure E 6 Efficacy of the vaccine against RV GE episodes with a score ≥X on the Clark scale from 2 weeks after Dose 3 up to Visit 6 – ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A
Y-axis has been cut at 0

Table E 23 Percentage of subjects reporting all cause GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

				n/N			Vaccine Efficacy			
					95%CI			95%CI		
Country	Group	N	n	%	LL	UL	%	LL	UL	P-value
Malawi	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
South Africa	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
All countries	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group in each country or overall
n/% = number/percentage of subjects reporting at least one GE episode regardless of any cause in each group
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table V.A

Table E 24 Percentage of subjects hospitalized and/or treated with re-hydration therapy due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized and/or treated with re-hydration therapy due to RV GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 25 Percentage of subjects hospitalized and/or treated with re-hydration therapy due to GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 - ATP cohort for efficacy

			n/N			Vaccine Efficacy			
				95%CI			95%CI		
Group	N	n	%	LL	UL	%	LL	UL	P-value
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

N = number of subjects included in each group
n/% = number/percentage of subjects hospitalized and/or treated with re-hydration therapy due to GE episode
95% CI, LL, UL = Lower and upper limits of the exact 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table V.A

Table E 26 Percentage of subjects reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6 by status of anti-rotavirus IgA antibody concentration after Dose 3 - ATP cohort for efficacy

Anti-rotavirus IgA antibody status at Visit 4				n/N			Vaccine Efficacy			
					95%CI			95%CI		
	Group	N	n	%	LL	UL	%	LL	UL	P-value
Positive	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Negative	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.
Unknown	HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
	Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	.	.	.	.

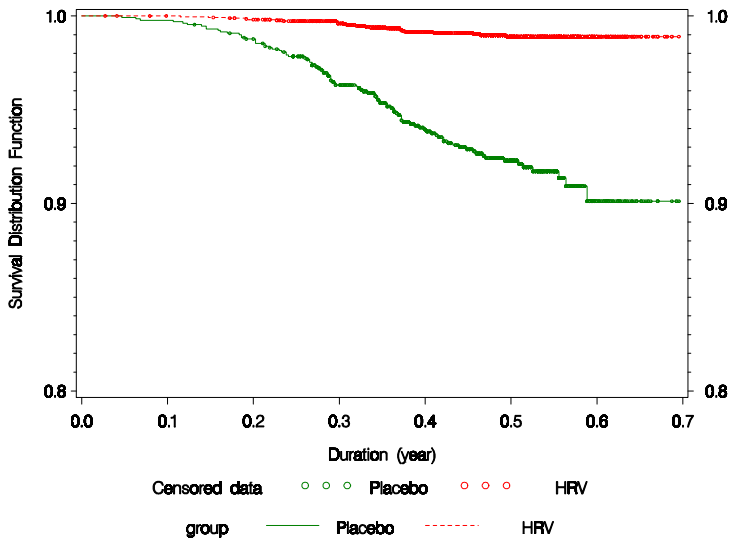
N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode, by status of anti-rotavirus IgA antibodies concentrations at Visit 4
95% CI,LL,UL = Lower and upper limits of the 95% confidence interval
p_value=two-sided exact p_value conditional to the number of episodes
Data Source= Appendix Table IVA and V.A

Table E 27 Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 3 up to Visit 6, by Cox - ATP cohort for efficacy

Group	N	n	T (year)	n/T value	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	P-value
Severe RV GE of any wild gtype										
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx				
Severe RV GE of G1 wild type										
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx				
Severe RV GE of pooled Non G1 (G2, G3, G4, ...)										
HRV_2D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_3D	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
HRV_POOL	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx
Placebo	Xxx	Xxx	Xxx	Xxx	Xxx	Xxx				

N = number of subjects included in each group
n = number of subjects reporting at least one specofoed severe RV GE episode
T= sum of follow-up period expressed in year censored at the first occurrence of sepecified severe RV GE episode
n/T= person-year rate of RV GE in each group
95% CI=95% Confidence interval; L.L =Lower limit; U.L = upper limit
Data Source= Appendix Table IVA and V.A

Figure E 7 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 3 up to Visit 6- ATP cohort for efficacy



Data Source= Appendix Table IVA and V.A

Table CTRS 1 Demography of CTRS – Pooled countries

Number of subjects	**HRV_2D**	**HRV_3D**	**Placebo**
Planned, N	Xxx	Xxx	Xxx
Randomised, N (Total Vaccinated Cohort)	Xxx	Xxx	Xxx
Completed, n (%)	Xxx	Xxx	Xxx
Total Number Subjects Withdrawn, n (%)	Xxx	Xxx	Xxx
Withdrawn due to Adverse Events, n (%)	Xxx	Xxx	Xxx
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	Xxx	Xxx	Xxx
Demographics	**HRV_2D**	**HRV_3D**	**Placebo**
N (Total Vaccinated Cohort)	Xxx	Xxx	Xxx
Females:Males	Xxx	Xxx	Xxx
Mean Age, months (SD)	Xxx	Xxx	Xxx
White/caucasian, n (%)	Xxx	Xxx	Xxx

Table CTRS 2 Number (%) of subjects with serious adverse events from Dose 1 up to Visit 7(Total vaccinated cohort)

All SAEs	**HRV_2D N = XXX**	**HRV_3D 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_3D N = XXX**	**HRV_2D N =XXX**	**PLACEBO N =XXX**
Subjects with any SAE(s), n(%) [n related]			

6. ANNEX 2: CRITERIA FOR ELIMINATING SUBJECTS FROM STAT ANALYSES

Provided as a separate document.

7. ANNEX 3: INTERIM ANALYSIS ROTA-037

7.1. Introduction

It is proposed to perform an interim analysis on the 2 South Africa cohorts on data as cleaned as possible. The results of the interim analysis will be shared within GSK and with PATH according to pre-specified criteria (see section 7.3, below). In the scenarios where the results are shared within GSK and with PATH, they will also be shared with external stakeholders and decision-makers (e.g., GAVI, ADIP Management Committee, WHO SAGE, etc.) in order to provide timely information regarding the efficacy of Rotarix.

The interim analysis will be based on all subjects from the total vaccinated cohort with follow-up 15 days after dose 3. Only severe wild-type RV GE's with onset beyond 15 days after dose 3 but before visit 6 at 1 year of age (severity=Vesikari score ≥11) will be included.

A blinded review of the database dated 15 Jan 2008 indicates that the interim analysis will include 35 subjects with severe wild-type RV GE. Based on the contribution of these cohorts in the study (70% of the total enrolled cohort), it is anticipated that the final ATP cohort analysis will include a total of 50 subjects with severe wild-type RV GE.

Note that considering the similar efficacy observed in previous efficacy studies and the distribution of GE type observed so far in this study, it is not expected that the VE will differ significantly according to the country (e.g. we do not expect to see 70% efficacy from South Africa versus 30% from Malawi).

The timings for the interim and final analyses are

- Interim: Mid March, 2008
- Final Year 1 follow-up: November 2008
- Final Year 2 follow-up: July 2009

7.2. Procedures for ensuring scientific integrity of the study conclusion

In order to ensure that the risk of erroneous recommendation is controlled and that the scientific integrity of the study is maintained,

1. An OBrien & Fleming alpha spending function will be used at the interim and the final analysis. Therefore based on the anticipated 35 and 50 cases at the interim and final analysis, a 2-sided 1.55% nominal type I will be used at the interim analysis. The 2-sided nominal type I at the final analysis should be 4.51% if the total number of cases is 50. It will be revised according to the actual number of cases at the final analysis.

2. The interim analysis will be conducted by an independent analysis center. Results will be disseminated to GSK & PATH only if they meet prespecified criteria, determined jointly by GSK & PATH. These criteria were based on the degree of confidence in the data, whether positive or negative, that would justify early sharing of data for decision-making.

7.3. Possible outcomes of the interim analysis

The possible outcomes of the interim analysis will be as follows:

- Case 1: Nominal 2 sided P-value < 1.55% ie lower limit (LL) of 2-sided 98.45% CI is above 0%: the interim analysis will have demonstrated statistically significant effect in South Africa (type I error=2.5%). In this case the results will be disseminated within GSK & to PATH. Note that this criterion corresponds to observing a VE above 58%.

Table 1

# of cases in placebo	Total # of cases	observed VE	98.45% CI	
			LL	UL
25	35	80.00%	49.53%	93.01%
24	35	77.08%	43.18%	91.65%
23	35	73.91%	36.17%	90.18%
22	35	70.45%	28.38%	88.57%
21	35	66.67%	19.67%	86.83%
20	35	62.50%	9.86%	84.92%
19	35	57.89%	-1.26%	82.84%
18	35	52.78%	-13.97%	80.56%

The power to meet this criterion and to conclude that VE is > 0% at the final analysis is shown below for different true VE:

Table 2

true VE	Power at interim	Power at final
90%	99.8%	99.8%
80%	97.7%	99.9%
75%	91.3%	99.8%
70%	79.8%	98.7%
65%	64.9%	95.5%
60%	49.5%	88.9%
55%	35.9%	78.9%
50%	25.0%	66.6%
45%	16.9%	53.6%

40%	11.1%	41.4%

- Case 2: Upper limit of 2-sided 95% CI is below 59% ie an observed VE <15%. The probability that this happens and the probability, would this happen, to conclude VE > 0% at the final analysis is shown below:

Table 3

True VE	Probability to get case 2 at the interim	Probability to get a LL for the 2 sided 96.49% CI for VE above 0% with 50 cases at final analysis if case 2 is met at interim
90%	0.00%	91.02%
80%	0.00%	56.48%
75%	0.00%	40.41%
70%	0.00%	28.01%
65%	0.10%	19.10%
60%	0.34%	12.93%
55%	0.92%	8.74%
50%	2.05%	5.92%
45%	3.89%	4.03%
40%	6.58%	2.77%

In this case, the results will be disseminated within GSK & to PATH as the final analysis will very likely be inconclusive.

- Case 3: In all other cases, the interim results will not be disseminated/shared with GSK or PATH. The power for the final analysis to conclude VE > 0% is shown in table 1 as follows:

true VE	Power at interim	Power at final
90%	99.8%	99.8%
80%	97.7%	99.9%
75%	91.3%	99.8%
70%	79.8%	98.7%
65%	64.9%	95.5%
60%	49.5%	88.9%
55%	35.9%	78.9%
50%	25.0%	66.6%
45%	16.9%	53.6%
40%	11.1%	41.4%

In all cases the study will proceed up to the final analysis including the Malawi cohort and no publication/abstract of the interim results will be released.

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.