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

*The following guiding principles have been applied to the disclosure:*

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

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

# GlaxoSmithKline Biologicals

## Study title

Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants.

## Study detailed title

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

# Clinical Study Report for Study 113808 (ROTA-075)

### Development Phase III

### IND Number: 2009L10238

**Indication Studied:** Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

| | |
|---|---|
| **Study initiation date:** | 29 August 2010 |
| **Study completion date:** | 12 May 2012 |
| **Data lock point (Date of database freeze):** | 31 August 2012 |
| **Date of report:** | Final: 29 October 2012 |
| **Report Scope:** | This clinical study report presents the final analysis of efficacy, safety and reactogenicity observed during the entire study period. |

**Sponsor Signatory:** [redacted]
Director, Lead Clinical Development,
DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development
GlaxoSmithKline Biologicals.

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

*GSK Biologicals' Study Report INS-BIO-CLIN-1010 v03*

# Foreword

**Study title**

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid HRV vaccine in healthy Chinese infants.

**Name of the Investigational Product:** GSK Biologicals' oral live attenuated HRV vaccine (Rotarix™).

**Name of the Sponsor:** GSK Biologicals, Rixensart, Belgium.

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| **Study Start Date** | 29 August 2010 |
| **Study End date** | 12 May 2012 |

**Name of the Principal Investigator:** Dr. [redacted]

**Address of the Study centre:** [redacted] China.

**Date of the study report**: 29 October 2012

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|---|---|
| **Name of the Sponsor contacts at GSK:** | [redacted] Director, Lead Clinical Development, DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development GlaxoSmithKline Biologicals. |

**Storage of source documents pertaining to the study:**

| | |
|---|---|
| **At the Investigator site:** | [redacted] hina |
| **At GSK China:** | 19, Shunchi Road, Beijing Airport Logistics Zone, Shunyi Distric, Beijing, 101300, China. |
| **At GlaxoSmithKline Biologicals:** | Not applicable |

**Summary of the Report: Please refer to the** SYNOPSIS (REPORT SUMMARY)**.**

# SYNOPSIS (REPORT SUMMARY)

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

**Study No.:** 113808 (ROTA-075)

**Title of the study:** A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

**Principal investigator**: This study was conducted at four centres and Dr. [redacted] was the Principal Investigator for the study.

**Study Centres:** This study was conducted at 4 centres in China.

**Publication (reference):** Not published as of : 29 October 2012

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|---|---|
| **Study period:**<br>**Study initiation date:** 29 August 2010<br>**Study completion date:** 12 May 2012<br>**Data lock point (Date of database freeze):** 31 August 2012 | **Phase:** III |

**Indication:** Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

**Treatment:**

The study groups were as follows:

- Group HRV vaccine (Planned, N = 1625)
- Group Placebo (Planned, N = 1625)

Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.

There were two sub-cohorts in this study as described below.

- Immunogenicity Sub-cohort 1 (N=600)
- Immunogenicity Sub-cohort 2 (N=300).

Subjects in each group received routine childhood vaccinations according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 received DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose.

**Objectives:** The study objectives considered for analyses presented in this study report are listed below. Immunogenicity objectives will be presented in a separate annex report.

**Primary**

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective was reached when the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy was at least 10%.

**Secondary**

***Efficacy:***

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation

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due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

**Reactogenicity and Safety:**

***All subjects except subjects in the immunogenicity sub-cohort 2:***

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

***Subjects in the immunogenicity sub-cohort 2:***

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

***All subjects:***

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

**Study design:**

This was a double-blind, randomised, placebo controlled, multi-centric and single-country study with two parallel groups (Group HRV vaccine and Group Placebo). Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1. The study comprised of 7 visits [Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2), Visit 4 (Month 3), Visit 5 (Month 4), Visit 6 (at approximately 1 year of age) and Visit 7 (at approximately 20 months of age) at end of the rotavirus season in China (approximately April 2012)]. Blood samples were to be collected from the sub-cohorts as follows:

- **Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600):**
  - Three blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1, at Visit 3and at Visit 6.
- **Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300)**:
  - Four blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1, at Visit 3, at Visit 5 and at Visit 6.

Active follow-up for the occurrence of GE* episodes was conducted during the study period via telephone contact or by other means (at least every 2 weeks).

*Note: GE was defined as diarrhoea with or without vomiting. As per the protocol, the final analysis was to be done once 40 severe RV GE episodes caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or at study conclusion, whichever was the earliest. Based on the preliminary review of GE episodes reported prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate during the first RV season seemed lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up was extended till approximately April 2012 (i.e. end of RV season in China).

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

*Vaccination schedule /site*: Subjects were to receive two oral doses of liquid HRV vaccine according to a 0, 1 month schedule.

*Vaccine composition /dose /lot number:* Each 1.5 ml dose of GSK Biologicals' liquid HRV vaccine contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$*) of RIX4414 HRV strain, Dulbecco's Modified Eagle Medium, Di-sodium Adipate and sucrose (w/w). Lot number AROLA219B, [Expiry date: 30 September, 2012] was used for the liquid HRV vaccination.

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**Reference vaccine /Comparator, dose and mode of administration, lot no.:**
*Vaccination schedule /site:* Subjects were to receive two oral doses of the placebo according to a 0, 1 month schedule.
*Vaccine composition /dose /lot number:* Each 1.5 ml dose of GSK Biologicals' placebo or liquid HRV vaccine contained 2.26 mg of DMEM, 132.74 mg of Di-sodium Adipate and 55% of sucrose (w/w). Lot number PROLA008A, [Expiry date: (31 October 2012)] was used for the placebo.

**Routine vaccines, dose and mode of administration, lot no.:**
*Vaccination schedule /site:* Subjects were to receive three doses of Diphtheria-tetanus- acellular pertussis (DTPa) vaccine as intramuscular injections.
*Vaccine composition /dose /lot number:* Each 0.5 ml dose of GSK Biologicals' DTPa vaccine (Infanrix™) contained Diphtheria toxoid ≥ 30 international units (IU), 25 Limits of flocculation (Lf), Tetanus toxoid ≥ 40 IU, (10Lf) Pertussis toxoid 25 µg, Filamentous haemagglutinin 25 µg, Pertactin 8 µg and Aluminium as salts 0.5 mg 2-phenoxyethanol ≤ 2.5 mg. Lot number (YC14B113AA), [Expiry date: 01 July, 2012] was used for the DTPa vaccination.
*Vaccination schedule /site:* Subjects were to receive three oral doses of Oral poliovirus vaccine (OPV) vaccine.
*Vaccine composition /dose /lot number:* Each dose of 0.1 ml (2 drops) of Institute of Medical Biology Chinese Academy of Medical Sciences' OPV contained Total polio-virus not less than 6.15lg $CCID_{50}$ type1, not less than 6.0 $lgCCID_{50}$, type2, not less than 5.0 $lgCCID_{50}$, type3, not less than 5.5 $lgCCID_{50}$. Lot number [20100202], [Expiry date: 01 February, 2012] was used for the OPV vaccination.

**Study Population (Selection of subjects):**
The study population included healthy male/ female infants of Chinese origin aged between 6 and 16 weeks (42-112 days) at the time of the first vaccination who were born after a gestation period of 36 to 42 weeks inclusive. Written informed consent was obtained from the parents/legally acceptable representatives (LARs) of these subjects.

**Duration of study:**
The subjects were followed for approximately 21 months i.e. from study start up to the study end.

The study endpoints considered for analyses presented in this study report are listed below. Immunogenicity endpoints will be presented in a separate annex report.

**Primary Outcome/Efficacy Variable:**

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

**Secondary Outcome/Efficacy Variables:**

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

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- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

*Reactogenicity and Safety:*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs:
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

**Statistical methods:**

***Demography:***

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 were calculated per group and overall. The racial and gender composition was presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall.

***Analysis of Efficacy***

The according-to-protocol (ATP) cohort for efficacy was used for the primary analysis of efficacy. An analysis of efficacy based on the total vaccinated cohort (TVC) was also performed.

During the efficacy follow-up period (2 weeks post Dose 2 to Visit 7 for the ATP cohort), vaccine efficacy was calculated, with their 95% CI against:

- severe RV GE caused by the circulating wild-type RV strains.
- any RV GE caused by the circulating wild-type RV strains.
- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains.
- any and severe RV GE due to each non-G1 type.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains.
- any and severe all cause GE.

Vaccine efficacy was also derived from a Cox regression model on the time to first event with censoring

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for subjects without an event as an additional supportive and exploratory analysis.
Vaccine efficacy analysis was also performed on the data collected from 2 weeks post Dose 2 of HRV vaccine /placebo up to Visit 6. This was presented as an additional supportive analysis.
The same analysis was also performed on Total Vaccinated Cohort from Dose 1 to Visit 6 and Dose 1 to Visit 7 (study end).

***Analysis of Safety (solicited AEs):***

The analysis of safety was based on the TVC. As the percentage of enrolled subjects excluded from the ATP cohort for safety was lower than 5% in both groups, analysis based on the ATP cohort was not performed.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) reported during the solicited follow-up period was tabulated by group, for each dose, for overall doses and per subject. The same calculations were performed for any grade 3 symptoms (solicited or unsolicited) and for any symptom (solicited or unsolicited) related to vaccination.
The incidence, with exact 95% CI, of each individual solicited general symptom, was calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations were done for each individual solicited general symptoms graded as intensity 3 and for each individual solicited general symptom casually related to vaccination. Note: Intensity of fever was assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale was performed separately.
The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term.

- Occurrence of fever was reported per 0.5°C cumulative temperature increments.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects for whom at least one local AE (solicited and unsolicited) was reported after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination were tabulated with exact 95% CI. The same calculations were performed for any grade 3 (solicited or unsolicited) symptoms, grade 3 related symptoms and for any symptoms that required medical attention.
- The percentage of subjects for whom each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa was reported during the 8-day (Days 0–7) follow-up period with exact 95% CI were tabulated.

***Analysis of Safety (unsolicited AEs and SAEs):***

**For all subjects:**

SAEs reported during the study period (i.e. from first vaccine dose to study end) were described in detail. There was a retrospective follow-up on SAEs for subjects who had already completed Visit 6 prior to the implementation of protocol amendment 2.
The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.
The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

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**Study population (Total vaccinated cohort)**

| **Number of subjects** | **HRV group** | **Placebo group** |
|---|---|---|
| Planned, N | 1625 | 1625 |
| Randomised, N (Total Vaccinated Cohort) | 1666 | 1667 |
| Completed, n (%) | 1518 (91.1) | 1499 (89.9) |
| **Demographics** | **HRV group** | **Placebo group** |
| N (Total Vaccinated Cohort) | 1666 | 1667 |
| Females: Males | 795:871 | 836:831 |
| Mean Age, weeks (SD) | 9.5 (2.64) | 9.7 (2.59) |
| Asian-Chinese heritage, n (%) | 1666 (100) | 1667 (100) |

SD=Standard deviation
Completed= number of subjects who completed last study visit

**Summary (Study results):**

Immunogenicity results will be presented in a separate annex report.

***Efficacy Results:***

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV was 72.0% [95% CI: 54.1%; 83.6%]. Severe RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (1.3% versus 4.8%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7. The primary objective of the study was met since the lower limit of the 95% CI on vaccine efficacy was above 10% (pre-specified criteria for the primary efficacy objective).
- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.1% [95% CI: 44.3%; 68.8%]. RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (4.4% versus 10.6%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating wild type G1 was 52.2% [95% CI: 19.0%; 72.6%] and 64.0% [95% CI: 20.4%; 85.2%], respectively. Vaccine efficacy against severe RV GE caused by circulating wild type G1P[8] was 60.1% [95% CI: 5.3%; 84.8%]. Vaccine efficacy against any RV GE caused by G1P[8] was 47.4% [95% CI: 7.4%; 71%, p-value 0.024].Fewer subjects in the HRV group reported any and severe RV GE caused by circulating wild-type G1 compared to the placebo group (1.4% and 0.6% versus 2.9% and 1.6% , respectively, p-value 0.005 and 0.009) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating non-G1 type was 62.1% [95% CI: 46.9%; 73.3%] and 77.8% [95% CI: 58.0%; 89.2%], respectively. Fewer subjects in the HRV group reported any and severe non-G1 type RV GE episode compared to the placebo group (3.1% and 0.8% versus 8.2% and 3.4%, respectively, p-value <0.001 for both) from 2 weeks post-Dose 2 up to Visit 7. Vaccine efficacy against any RV GE caused by G2P[4] was 58.9% [95% CI: 40.5%; 72.0%, p-value <0.001].Vaccine efficacy against severe RV GE caused by G2P[4] was 72.5% [95% CI: 45.5%; 87.3%].
- Vaccine efficacy against RV GE caused by circulating wild-type RV that required hospitalization was 81.0% [95% CI: 43.6%; 95.3%]. Fewer subjects in the HRV group required hospitalization following an episode of RV GE as compared to the placebo group (0.3% versus 1.3%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against RV GE leading to hospitalization or requiring rehydration therapy was 66.4% [95% CI: 49.6%; 78.1%]. Fewer subjects in the HRV group were hospitalized and/or

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required rehydration therapy following an episode of RV GE as compared to the placebo group (2.1% versus 6.2%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.

- Vaccine efficacy against all cause GE was 4.2% [95% CI: -6.2%; 13.6%]. All cause GE episodes reported for subjects in HRV group and placebo group was similar (46.2% versus 48.3%, p-value 0.422) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause severe GE was 9.3% [95% CI: -11.1%; 26.0%]. All cause severe GE episodes for subjects in HRV group and placebo group was similar (11.92% versus 13.1%, p-value: 0.357) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause GE that required hospitalization was 41.2% [95% CI: 13.1%; 60.6%]. Fewer subjects in the HRV group required hospitalization following an episode of all cause GE as compared to the placebo group (2.7% versus 4.6%, p-value 0.007) from 2 weeks post Dose 2 up to the Visit 7.

Percentage of subjects for whom severe (Vesikari score greater than or equal to 11) RVGE episode was reported and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 21 | 1.3 | 0.8 | 2.0 | 72.0 | 54.1 | 83.6 | <0.001 |
| Placebo | 1573 | 75 | 4.8 | 3.8 | 5.9 | - | - | - | - |

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

***Reactogenicity and Safety Results:*** The analysis of safety was performed on the Total vaccinated cohort.
***Any Symptom:***

**All subjects except immunogenicity sub-cohort 2:**

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any AEs (solicited or unsolicited) was 44.2% [95% CI: 41.7%; 46.8%] subjects in the HRV group and 47.3% [95% CI: 44.8%; 49.8%] subjects in the placebo group. Any AEs (solicited or unsolicited) were reported for 32.8% [95% CI: 30.4%; 35.2%] and 26.6% [95% CI: 24.4%; 29.0%] subjects after the first and second dose of HRV vaccine respectively. Any AEs (solicited or unsolicited) assessed as causally related to vaccination were reported by 15.8% [95% CI: 14.0%; 17.7%] subjects in HRV group and 14.7% [95% CI: 12.9%; 16.5%] subjects in the placebo group. No more than 11.2% of the subjects in both groups reported any AEs (solicited or unsolicited) rated as grade "3" in intensity.

**All subjects in the immunogenicity sub-cohort 2:**

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any general symptoms (solicited or unsolicited) was 52.9% [95% CI 44.7%; 61.1%] subjects in the HRV group and 50.3% [95% CI: 42.1%; 58.5%] subjects in the placebo group. Any general symptoms (solicited or unsolicited) were reported for 42.5% [95% CI: 34.5%; 50.7%] and 30.0% [95% CI: 22.8%; 38.0%] subjects after the first and second dose of HRV vaccine, respectively. No more than 16.0% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.

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- During the 8-day follow-up period (Day 0 to Day 7), any general symptoms (solicited or unsolicited) rated as grade "3" in intensity and causally related to vaccination were reported for 2.6% [95% CI: 0.7%; 6.6%] subjects in the HRV group and 2.0% [95% CI: 0.4%; 5.6%] subjects in the placebo group. No more than 1.3% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.
- During the 8-day follow-up period (Day 0 to Day 7), any AEs (solicited or unsolicited) requiring medical attention were reported for 12.4% [95% CI: 7.6%; 18.7%] subjects in the HRV group and 11.1% [95% CI: 6.6%; 17.2%] subjects in the placebo group.

***Solicited symptoms:***

**All subjects except immunogenicity sub-cohort 2:**

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 27.4% subjects in the HRV group and 29.6% subjects in the placebo group. Irritability/fussiness was reported for 21.5% [95% CI: 19.4%; 23.6%] and 12.9% [95% CI: 11.2%; 14.7%] subjects after the first and second dose of HRV vaccine, respectively.

**All subjects in the immunogenicity sub-cohort 2:**

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 36.6% subjects in the HRV group and 34.0% subjects in the placebo group. Irritability/fussiness was reported for 28.8% [95% CI: 21.7%; 36.6%] and 18.7% [95% CI: 12.8%; 25.8%] subjects after the first and second dose of HRV vaccine, respectively. No more than 3.3% of the subjects in both groups reported irritability/fussiness rated as grade "3" in intensity.
- During the 8-day (Day 0- Day 7) follow-up period, redness was the most frequently reported solicited local symptom for 13.3% subjects in the HRV group and 8.6% subjects in the placebo group. The most frequently reported grade "3" solicited local AEs were pain for 1.3% of subjects in the HRV group and redness for 0.7% of subjects in the placebo group. The solicited local symptoms were related to DTPa vaccine given intramuscularly.

**All subjects:**

***Unsolicited symptoms:***

- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 18.6% in the HRV group and 22.1% in the placebo group.
- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one grade "3" unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 0.1% in the HRV group and 0.2% in the placebo group. The percentage of subjects reported for unsolicited AEs assessed as causally related to vaccination was 0.5% in the HRV group and 0.4% in the placebo group.

***Serious adverse events:***

- During the study period, the percentage of subjects reported for at least one SAE was 11.0% (183/1666) in the HRV group and 14.8% (246/1667) in the placebo group. [redacted] None of the SAEs reported in the HRV group were causally related to the vaccine as assessed by the investigator. [redacted]
- Of the 13 deaths (6 in the HRV group and 7 in the placebo group) reported during the study period,

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

none of the fatal SAEs were assessed as causally related to vaccination by the investigator.

***Withdrawals due to adverse events /serious adverse events:***

- Eighteen subjects (8 in the HRV group and 10 in the placebo group) experienced unsolicited AEs or SAEs, leading to premature discontinuation from the study.

**Conclusion:**

Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV during the efficacy follow up period (2 weeks post-Dose 2 up to Visit 7) was 72.0% [95% CI: 54.1%; 83.6%]. The primary objective of this study was met.

**Date of report:** Final: 29 October 2012

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ATP** | According-To-Protocol |
| **$CCID_{50}$** | Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells) |
| **CI** | Confidence Interval |
| **DMEM** | Dulbecco's Modified Eagle Medium |
| **DTPa** | Combined Diphtheria, Tetanus and acellular Pertussis vaccine |
| **eCRF** | electronic Case Report Form |
| **$ED_{50}$** | Estimated dose 50% |
| **EL.U/mL** | ELISA Units per Millilitre |
| **ELISA** | Enzyme Linked Immunosorbent Assay |
| **EPI** | Expanded Program on Immunisation |
| **FHA** | Filamentous Haemagglutinin |
| **GCP** | Good Clinical Practice |
| **GE** | Gastroenteritis |
| **GMC** | Geometric Mean Concentration |
| **GSK** | GlaxoSmithKline |
| **GSM** | Global Study Manager |
| **HRV** | Human Rotavirus |
| **IB** | Investigator Brochure |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IgA** | Immunoglobulin A |
| **IM** | Intramuscular |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **IS** | Intussusception |
| **IU/mL** | International Units per Millilitre |
| **LAR** | Legally Acceptable Representative |
| **MedDRA** | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| **Mg** | Milligram |
| **mL** | Millilitre |
| **MMWR** | Morbidity and Mortality Weekly Report |
| **NIFDC** | National Institute for Food and Drug Control |
| **O** | Oral |
| **OPV** | Oral Poliovirus vaccine |
| **PCR** | Polymerase Chain Reaction |
| **PRN** | Pertactin |
| **PT** | Pertussis toxoid |
| **RV** | Rotavirus |
| **SAE** | Serious Adverse Event |
| **SAS** | Statistical Analysis System |
| **SBIR** | Internet Randomisation tool |
| **SDV** | Source Document Verification |
| **SFDA** | State Food and Drug Administration |
| **SPM** | Study Procedures Manual |
| **U/mL** | Units per Millilitre |
| **UA** | Upper Arm |
| **UMV** | Universal Mass Vaccination |
| **VE** | Vaccine Efficacy |
| **WHO** | World Health Organisation |

## GLOSSARY OF TERMS

| | |
|---|---|
| **According-To-Protocol cohort:** | This cohort included all subjects enrolled in the study who meet the criteria defined in the protocol for the considered analysis (Efficacy, reactogenicity and safety). |
| **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.<br><br>An AE was therefore 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 included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. |
| **Blinding:** | A procedure in which one or more parties to the trial were kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. 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. The level of blinding was maintained throughout the conduct of the trial, and only when the data were cleaned to an acceptable level of quality appropriate personnel unblinded or when required in case of a serious adverse event (SAE). |
| **Child in care:** | A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted nor has an appointed legal guardian. |
| **Completed:** | Subjects who were available for the study concluding visit. |
| **Diarrhoea:** | Passage of three or more looser than normal stools within a day. |

| | |
|---|---|
| **Diary card:** | Cards given to the parents /guardians by the investigator to record adverse events following vaccination. |
| **Eligible:** | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |
| **Epoch:** | An epoch was a self-contained set of consecutive time-points or a single time-point from a single protocol. Self-contained meant that data collected for all subjects at all time-points within that epoch allowed to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety. |
| **eTrack:** | GSK's tracking tool for clinical trials. |
| **Evaluable:** | Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis. |
| **Gastroenteritis:** | Diarrhoea with or without vomiting. |
| **Investigational vaccine/product:**<br><br>**(Synonym of Investigational Medicinal 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. |
| **Legally Acceptable Representative:** | ICH GCP defines Legally Accepted Representative (LAR) as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. |
| **Protocol amendment:** | The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study. |
| **Randomisation:** | Process of random attribution of treatment to subjects in order to reduce bias of selection. |

| | |
|---|---|
| **Serious adverse event:** | 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 event 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. |
| **Severe rotavirus gastroenteritis:** | An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system). |
| **Solicited adverse events:** | AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events was actively solicited from the subject's parent/LAR or an observer during a specified post-vaccination follow-up period. |
| **Sub-cohort:** | A group of subjects for whom specific data are collected compared to other subjects. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Subject:** | Term used throughout the clinical study report to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control. |
| **Symptom sheet:** | Specific pages in the individual case report form onto which the investigator transcribed from the diary card and/or other source documentation on solicited adverse event(s) reported by the parents /guardians (one sheet for solicited local adverse events, one sheet for solicited general adverse events). |
| **Total vaccinated cohort:** | The total vaccinated cohort will include all subjects with at least one vaccine administration documented. A safety analysis based on the total vaccinated cohort will include all vaccinated subjects. An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available. |
| **Treatment number:** | A number identifying a treatment to a subject, according to the study randomisation or treatment allocation. |

| | |
|---|---|
| **Treatment:** | Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation. |
| **Unsolicited adverse event:** | Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms were reported as an unsolicited adverse event. |
| **Vomiting:** | One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day. |

## TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the Study Report (including the synopsis), the names of the vaccines/products and/or medications will be written without the superscript symbol ™ or ® and in *italics*.

| Trademarks of the GlaxoSmithKline group of companies | Generic description |
|---|---|
| Rotarix™ | Human rotavirus vaccine |
| Infanrix™ | Combined diphtheria-tetanus-acellular pertussis (DTPa) vaccine |

| Trademarks not owned by the GlaxoSmithKline group of companies | Generic description |
|---|---|
| OPV (Institute of Medical Biology Chinese Academy of Medical Sciences') | Poliomyelitis (live) Vaccine (Monkey Kidney Cell), Oral |

# 1. ETHICS

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

The study protocol, two amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre IEC.

## 1.2. Ethical conduct of the study

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

## 1.3. Subject information and consent

Written informed consent was obtained from the parent/ legally acceptable representative (LAR) prior to the performance of any study-specific procedures. Electronic case report forms (eCRFs) were provided for each subject's data to be recorded.

# 2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE (STUDY MANAGEMENT)

## 2.1. Administrative structure

This study was conducted at 4 centres in China by Dr. [redacted] as the principal investigator.

**Responsibilities of the Investigator:**

- Compliance with GCP procedures and applicable local regulations in China.
- Permitting monitoring and auditing by GSK or a GSK designated organisation.
- Maintenance of a list of appropriately qualified persons to whom trial-related duties were delegated.

In terms of the Investigator resources *(ICH-GCP 4.2)*:

- Potential for recruiting potential subjects
- Sufficient time to conduct the trial
- Qualified personnel and adequate training of study personnel
- Adequate facilities at the study centre to conduct the trial.

In terms of obtaining approval from the appropriate IRB/IEC *(ICH-GCP 4.4)*:

Before initiating the trial, the Investigator had to write and date the approval for:

- The trial protocol,
- Written informed consent form and consent form updates (if any),
- Subject recruitment procedures (e.g. advertisements),
- Any other information that was to be provided to the subjects,
- Investigator brochure.

In terms of medical care of trial subjects *(ICH-GCP 4.3)*:

- A qualified physician (Investigator or sub investigator) was responsible for all trial-related medical decisions.

In terms of compliance with the protocol *(ICH-GCP 4.5):*

- The Investigator/Institution was to sign the protocol, or an alternative contract, to confirm agreement to comply with the protocol and was not to implement any deviations without:
  - agreement by the Sponsor,
  - prior review and documented approval from the IRB/IEC of an amendment,
  - except, where necessary to eliminate an immediate hazard(s) to trial subjects or,
  - when changes involved only logistical or administrative aspects of the trial.

In terms of accountability of the investigational product *(ICH-GCP 4.6)*:

- Accountability of the investigational product at the trial site was the sole responsibility of the Investigator, for which the Investigator was to maintain adequate documentation that:
  - doses were provided to subjects as specified in the protocol,
  - reconciliation of all investigational products received from the Sponsor,
  - the investigational product was to be stored and used as specified in the protocol.

In terms of maintenance of trial-related records and reports *(ICH-GCP 4.9.5)*:

- Records were to be accurate, complete, legible and timely pertinent to the data reported [i.e. subjects' hospital records, eCRFs].
- Data reported on the eCRFs were to be derived from the source document.

- All corrections to an eCRF were to be dated, initialed, explained and were not to obscure the original entry.
  **Note**: eCRFs were used in this study and the Remote Data Entry (RDE) application used a built-in system to track any corrections to data.
- The period of retention of all documents was a minimum of 2 years after the last approval of marketing application of the product.
- The Investigator was to permit direct access to all trial-related records and reports to the Sponsor (auditor, monitor), IRB/IEC and regulatory authorities.

In terms of communication with the IRB/IEC:

During trial period, investigator was to forward to the IRB/IEC:

- investigator brochure updates
- written summaries on the status of the trial annually or more frequently (if it was requested)
- the Investigator was to provide written progress reports to the Sponsor and the IRB/IEC on any changes that significantly affected the trial or increased risk to subjects.

If the Investigator terminated or suspended the trial without prior agreement of the Sponsor, the Investigator was to provide detailed written explanation to the Sponsor, the IRB/IEC and the regulatory authorities (if required).

In case premature termination or suspension of a trial the Investigator was to inform trial subjects and assure appropriate therapy and follow-up.

After completion of the trial, the Investigator was to inform and provide the Sponsor, the IRB/IEC all the required reports, a summary of the study outcome and reports to regulatory authorities (if applicable).

Additionally, the Investigator was also responsible for:

- The review of the consent form and appropriate consent procedure *(ICH-GCP 4.8)*
- Reporting of serious adverse events (SAEs) to Sponsor and the IRB/IEC and notification of investigator brochure updates to IRB/IEC *(ICH-GCP 4.11)*.

**Responsibilities of the Study Sponsor:**

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

In terms of implementing and maintaining Quality Assurance (QA) and Quality Control (QC) systems:

- The Sponsor was to ensure that the trial was conducted, data generated and documentation of data (data were reliable and processed correctly) and reported data was in compliance with the protocol, GCP and regulatory requirements.
- The Sponsor was to secure a written agreement with the Investigator (institution and/or parties involved in the clinical trial) to the trial-related site, source data/documents and reports, primarily for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.
- If the Sponsor transferred any trial-related duties and functions to a Contract Research Organisation (CRO), it was the Sponsor's responsibility to ensure:
  - Quality and integrity of trial data. It was the function of the CRO to implement QA and QC
  - Clear explanation of functions that were "not" transferred to the CRO, including the duties and functions of the Sponsor.
- The Sponsor was to designate qualified medical personnel to answer any trial-related medical queries. The Sponsor was also to appoint qualified personnel (biostatisticians, physicians etc) for:
  - designing protocols and eCRFs, analysing data, and for preparation of clinical trial reports/study reports
  - Supervision of the trial and handling and verification of data.
- The Sponsor was to provide guidance to the Investigator on the clinical trial protocol and protocol amendments, including ICH guidance on the structure of the clinical trial.
- For trial management, the Sponsor was to provide Subject Identification Code and retain all Sponsor-specific essential documents.
- In case of discontinuation (termination/suspension) of the clinical trial, the Sponsor was to provide a written explanation to the Investigator and the IRB/IEC.
- In case of transfer of ownership of the trial, the Sponsor was to report this to the relevant authority.
- The Sponsor was to inform the Investigator/Institution that all trial-related documents were to be retained for a minimum of 2 years after the last approval of marketing application of the investigational product. The Sponsor was also to inform the Investigator/Institution regarding the destruction of any documents.
- In terms of selection of the Investigator/Institution for the trial, the Sponsor was to:
  - Select qualified personnel (with experience and resources to conduct the trial). For multicentre trials, the Sponsor was to select a coordinating committee and/or coordinating investigator(s)
  - provide the protocol and the investigator brochure (that included non-clinical/ clinical data)

  - Obtain the Investigator's/Institution's agreement to conduct the trial according to GCP (after obtaining approval from the IRB/IEC), to comply with procedures, to permit monitoring, auditing and inspection and to retain essential documents.

- All trial-related duties and functions were to be defined and established by the Sponsor.
- In terms of providing compensation to the subjects and Investigators, the Sponsor was to:
  - provide insurance against claims arising from the trial (except for malpractice and/or negligence)
  - address costs of treatment (of subjects) i.e. during trial-related injuries
  - Compensation of trial subjects in compliance with applicable regulatory requirement(s).
- The Sponsor was to inform the Investigator/Institution of all financial aspects related to the trial in an agreement.
- The applications required for the trial were to be submitted/notified by the Sponsor to the appropriate authority(ies) for review, acceptance and/or for permission to start the trial.
- For confirmation of review of relevant documents by the IRB/IEC, the Sponsor was to obtain the name and address of the IRB/IEC, if it operated according to GCP and the applicable laws and regulations in the country. The Sponsor was to ensure that there was documentation for the IRB/IEC approval for the protocol, written informed consent form(s), written information provided to subjects, subject recruiting procedures, and documents related to payments.
- The Sponsor was to obtain from Investigator/ Institution a copy of the modification(s) made and the approval date given by the IRB/IEC.
- The Sponsor was to ensure that the investigational product was manufactured according to Good manufacturing Practices with appropriate coding and labeling of products to maintain blinding and identification.
- The Sponsor was to ensure that the investigational product was sent to the investigational site(s) after obtaining appropriate documentation.
- The Sponsor was to ensure that the Investigator/Institution maintained the investigational product under defined storage conditions.
- The Sponsor was to provide written procedures to the Investigator/Institution for the adequate and safe receipt, handling, storage, and dispensing, retrieval of unused investigational product, and return of unused investigational product to the Sponsor (or alternative disposition).
- The Sponsor was to ensure timely delivery of the investigational product. Maintain records for the shipment, receipt, disposition, return and destruction of the investigational product. The Sponsor was to maintain documentation in case the investigational product was retrieved due to expiry or after trial completion.

- The Sponsor was to ensure investigational product stability over the period of use.
- The Sponsor was to provide specifications to the Investigator/Institution for providing direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. This also included access to written informed consent of subjects, direct access to original medical records, audit, IRB/IEC review, and regulatory inspection.
- The Sponsor was to evaluate safety data from the trial regularly and inform the Investigator/Institution and regulatory authority(ies) in case findings affected the safety of subjects in the trial.
- For adverse drug reporting, the Sponsor was to submit safety reports and periodic reports to the regulatory authority(ies).
- The Sponsor was to evaluate trial conduct and compliance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirements by conduct of audits, as appropriate.
- In case of non-compliance to the protocol, SOPs, GCP and/or applicable regulatory requirements by the Investigator/Institution or members of the Sponsor's staff, the Sponsor was to take prompt action.

The Sponsor was to ensure that clinical trial study reports were prepared and provided to the regulatory authority (ies).

# 3. INTRODUCTION

## 3.1. Background

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) among young children aged < 5 years. A recent review estimated that RV is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year where the majority of the deaths occur in the developing countries in Asia and Africa [WHO, 2007].

China has the second largest birth cohort in the world and the second highest number of deaths due to RV infection. In China, RV is the most common cause of diarrhoea and an economic burden for the parents. Approximately 27, 000 RV associated deaths occur each year and 32% - 50% of the hospitalised diarrhoea are associated with an RV infection [Naghipour, 2008; Wang, 2009].

In China, introduction of a RV vaccine would most likely be beneficial for children and a significant proportion of the diarrhoeal disease burden might be prevented in the near future [Liu, 2006].

GlaxoSmithKline (GSK) Biologicals had developed a human rotavirus (HRV) vaccine to meet this health need. GSK Biologicals' lyophilised HRV vaccine has been extensively tested in clinical studies conducted in infants from Europe, North America, Latin America and the Caribbean, Asia and Africa. In addition to the lyophilised formulation, GlaxoSmithKline (GSK) Biologicals had also developed a liquid formulation of the human rotavirus (HRV) vaccine.

Please refer to the current Investigator Brochure for a review of the pre-clinical and clinical studies, and the potential risks and benefits of liquid HRV vaccine.

## 3.2. Rationale on study design, vaccine administration schedule and indication

### 3.2.1. Rationale for the study

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of file for licensure in China.

### 3.2.2. Rationale for the study design

This phase III, double-blind, randomised, placebo-controlled, multi-centre study was conducted to assess the efficacy, immunogenicity and safety of GSK Biologicals' liquid HRV vaccine. GSK Biologicals also intends to submit immunogenicity and reactogenicity data of the co-administered routine vaccines to the Chinese State Food and Drug Administration (sFDA). In order to assess the immunogenicity of HRV vaccine and the co-administered routine vaccines, two immunogenicity sub-cohorts were planned to be enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo was to be

assessed in the first sub-cohort (N = 600). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 was to be assessed in the second sub-cohort (N = 300). Reactogenicity of the liquid HRV vaccine/Placebo was assessed in the whole cohort except for the second immunogenicity sub-cohort.

# 4. STUDY OBJECTIVES (PURPOSE OF THE STUDY)

The study objectives considered for analyses presented in this study report are listed below. Immunogenicity objectives will be presented in a separate annex report.

## 4.1. Primary objective

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy is at least 10%.

## 4.2. Secondary objectives

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

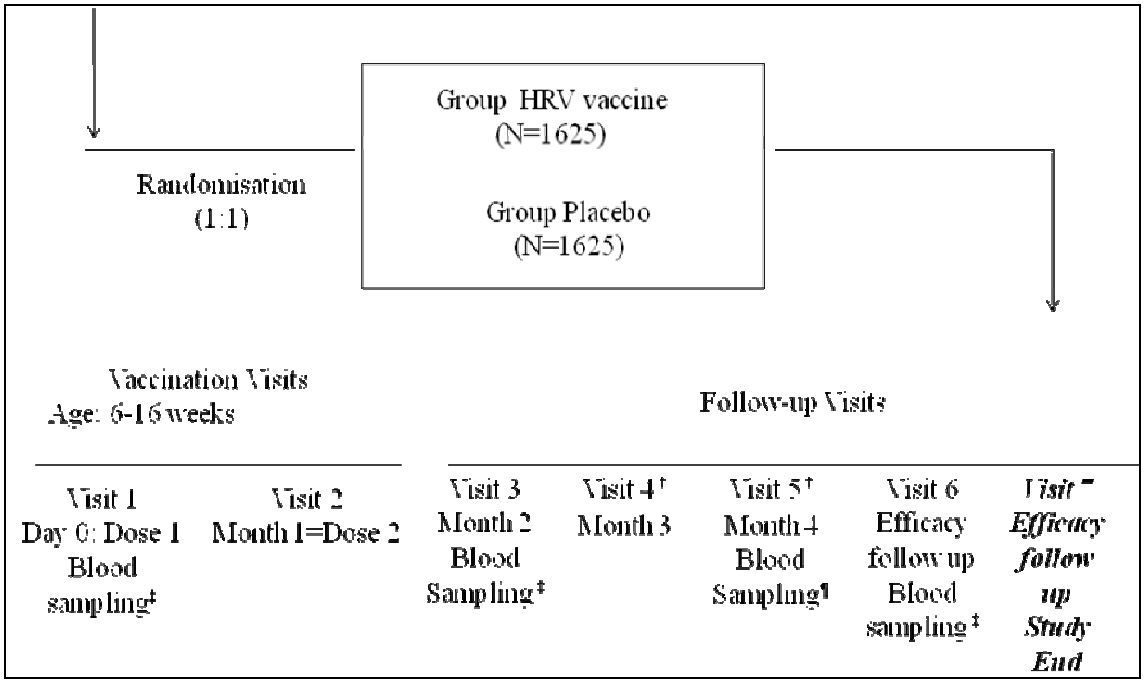
*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

See Section 5.9 for details of the study endpoints.

# 5. INVESTIGATIONAL PLAN

## 5.1. Study design (Overview and description of the protocol)




N: Number of subjects that was planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 was applicable only to subjects in the immunogenicity sub-cohort 2.
‡Blood was drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood was drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 received a dose of OPV at Visit 1, Visit 2 and Visit 3; and received a dose of DTPa at Visit 2, Visit 3 and Visit 4.

### 5.1.1. Overall study design – Description (Discussion of study design)

- Experimental design: Phase III, double-blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: The subjects were to be followed from study start until approximately April 2012 (i.e. end of RV season in China). The duration of the study, per subject, did not exceed a maximum of 21 months. The study had a single epoch as follows.
  - Primary Epoch: Primary epoch started at Visit 1 (Day 0) and ended at Visit 7 (approximately April 2012 i.e. end of RV season in China).

Table 1 presents the study groups and the epoch foreseen in the study.

**Table 1 Study groups and epochs foreseen in the study**

| Study group | Number of subjects | Age in weeks (MIN/Max) at Dose 1 | Epoch |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 – 16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedules: Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.
  - Subjects in each group were to receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 were to receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study were documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (Planned, N = 1625)
  - Group Placebo (Planned, N = 1625)

The treatment groups for the study are presented in Table 2.

**Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine were given concomitantly with liquid HRV Vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

- Treatment allocation: Randomised with balanced allocation (1:1).
- Blinding**:** Double-blind study.
- Blood Sampling: Blood samples were to be collected from two sub-cohorts of subjects.
  - Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).
  - Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) reported after each dose of liquid HRV vaccine/placebo, using diary cards (was applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) reported after each dose of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (was applicable only for subjects in the immunogenicity sub-cohort 2).
- Unsolicited AEs were followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV vaccine/placebo.
- Recording of SAEs throughout the study period for all subjects.
  - for subjects who had completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs was done.
- Active follow-up for occurrence of GE* episodes was conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE was defined as diarrhoea with or without vomiting.
- For each GE episode occurring during the study period,
  - a GE diary card was completed daily until end of the GE symptoms.
  - a stool sample was collected as soon as possible after GE symptoms begin.
  - for subjects who had completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes was done.

- Parents/LARs of the subjects (including those subjects who had completed Visit 6 prior to the implementation of protocol amendment 2) were contacted to ask if their children would participate in the extended follow-up (Visit 7).
- An additional informed consent was taken for the extended follow-up.
- Type of study: self-contained.
- Data collection: eCRF.
- Final analysis was to be done as per protocol, when 40 severe RV GE episodes caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or at study conclusion, whichever was the earliest.

## 5.2. Study procedures

### 5.2.1. Outline of study procedures

Table 3 presents the list of study procedures.

**Table 3 List of study procedures**

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | Visit 7 |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | years 1 of age | April 2012[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | Efficacy follow up |
| Informed consent | ● | | | | | | |
| Re-consenting for Visit 7 follow-up | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | ○ | ○ | ○ | ○ | ○ | ○ |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approxi-mately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approxi-mately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approxi-mately 3mL: sub-cohort 2) | ● (Approxi-mately 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+ DTPa) | ● (OPV+ DTPa) | ● (DTPa) | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | Visit 7 |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | years 1 of age | April 2012[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | Efficacy follow up |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of unsolicited AEs within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | ○ | ○ | ○ | ○ | ○ | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

● used to indicate a study procedure that required documentation in the individual eCRF.
○ used to indicate a study procedure that did not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 were applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
[β]i.e. end of the RV season in China.

## 5.2.2. Intervals between study visits

Table 4 presents the intervals between study visits.

### Table 4 Intervals between study visits

| Interval | Optimal length of interval[1] | Maximum interval allowed[2] |
|---|---|---|
| 1 (Visit 1)→(Visit 2) | 30-48 days | 21-48 days |
| 2 (Visit 2)→(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3)→(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | 1 year of age± 2 weeks[γ] | 1 year of age ± 30 days |
| 6 (Visit 6) → (Visit 7) | 01 April 2012 to 30 April 2012[γ] | 01 April 2012 to 31 May 2012 |

[1]. Whenever possible the investigator arranged study visits within this interval
[2]. Subjects were not eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they made the study visit outside this interval
[γ] It was a defined time point for follow up visit in a range and not an interval.
Note: The date of the previous visit served as the reference date for intervals between study visits.

## 5.3. Selection of study population (Number of cases)

Target enrolment was 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated rate of non-evaluable subjects was 20%.

### 5.3.1. Inclusion criteria for enrolment (Selection of subjects)

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

- Subjects who the investigator believed that their parents/Legally Acceptable Representatives (LARs) could and would comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent/LARs of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of 36 to 42 weeks inclusive.

### 5.3.2. Exclusion criteria (Selection of subjects)

The following criteria were checked at the time of study entry. If **ANY** exclusion criterion was applicable, the subject was not included in the study:

- Child in care.

  Refer to the GLOSSARY OF TERMS for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone ≥ 0.5 mg/kg/day, or equivalent, inhaled and topical steroids were allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccines and ending 14 days after the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or would be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

- Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for Intussusception (IS).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness.
- History of confirmed RV GE.
- Acute disease and/or fever at the time of enrolment.
  - Fever was defined as temperature ≥37.1°C on axillary setting as defined by the Chinese authorities.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).
- GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

In addition to the criteria mentioned above, the following criteria were applicable to all subjects in the immunogenicity sub-cohort 2:

- History of diphtheria, tetanus and pertussis disease.
- History of seizures or progressive neurological disease.
- Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

### 5.3.3. Elimination criteria

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

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this meant prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and 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 the liquid HRV vaccine/placebo and ending 14 days after, with the exception of routine childhood vaccinations.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition likely to alter the immune response or are confirmed to have an immunodeficiency condition.

### 5.3.4. Contraindications to subsequent vaccination

***GSK Biologicals' liquid HRV vaccine or placebo:***

The following events constituted absolute contraindications to further administration of the liquid HRV vaccine or placebo. If any of these events occurred during the study, the subject did not receive additional doses of the vaccine but continued other study procedures at the discretion of the investigator.

- Hypersensitivity reaction following the administration of the liquid HRV vaccine or placebo.
- Intussusception (IS) and any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following events constituted contraindications to administration of liquid HRV vaccine and placebo at that point in time; if any of these events occurred at the time scheduled for vaccination, the subject was vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator.

- Acute disease at the time of vaccination. Acute disease was defined as the presence of a moderate or severe illness with or without fever. (Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.) All vaccines could be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness.
- GE within 7 days preceding the study vaccine administration.

***GSK Biologicals' DTPa vaccine:***

- DTPa vaccine was not administered to subjects with known hypersensitivity to any component of the vaccine or to subjects who showed signs of hypersensitivity after previous administration of DTPa vaccine.
- DTPa vaccine was contra-indicated if the child had experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with

pertussis containing vaccine. In these circumstances the vaccination course was continued with diphtheria and tetanus vaccine.

### 5.3.5. Warnings and precautions

*Warnings and precautions related to the liquid HRV vaccine*

The liquid HRV vaccine was under no circumstances to be injected.

*Warnings and precautions related to the DTPa*

It is good clinical practice that immunisation was preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of DTPa vaccine was to be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, was not a contra-indication.

If any of the following events occurred in temporal relation to receipt of DTPa, the decision to give subsequent doses of vaccine containing the pertussis component was carefully considered. There may have been circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events were not associated with permanent sequelae.

The following events were previously considered contra-indications for Diphtheria Tetanus whole cell Pertussis (DTPw) and are now considered general precautions:

- Temperature of ≥ 40.5°C within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

- In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it was better to defer pertussis (Pa) immunisation until the condition was corrected or stable. However, the decision to give pertussis vaccine was to be made on an individual basis after careful consideration of the risks and benefits.
- A history of febrile convulsions and a family history of convulsive fits did not constitute contra-indications.
- HIV infection was not considered as a contra-indication.
- As with all injectable vaccines, appropriate medical treatment was readily available in case of anaphylactic reactions followed by the administration of the vaccine. For

this reason, the vaccinee remained under medical supervision for 30 minutes after immunisation.

- As for all diphtheria, tetanus and pertussis vaccines, the vaccine was to be given deep intramuscularly and preferably at alternate injection sites.
- DTPa vaccine was to be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding could occur following an intramuscular administration to these subjects.
- DTPa vaccine was under no circumstances administered intravenously.
- The potential risk of apnoea and the need for respiratory monitoring for 48-72h was to be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination was high in this group of infants, vaccination was not withheld or delayed.

For warnings and precautions related to the OPV vaccines, please refer to the respective product labels/package inserts.

## 5.3.6. Subject completion and withdrawal

### 5.3.6.1. Subject completion

A subject who returned for the concluding visit in the protocol was considered to have completed the study.

### 5.3.6.2. Subject withdrawal

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

Withdrawals were not replaced.

#### *5.3.6.2.1. Subject withdrawal from the study*

From an analysis perspective, a ‘withdrawal’ from the study referred to any subject who did not come back for the concluding visit was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject was used for the analysis.

A subject was considered 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 documented in the eCRF. The investigator documented whether the decision to withdraw a subject from the study was made by the subject's parents/ LARs, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

#### *5.3.6.2.2. Subject withdrawal from investigational vaccine*

A 'withdrawal' from the investigational vaccine referred to 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 vaccine was not necessarily withdrawn from the study as further study procedures or follow-up could be performed (safety or immunogenicity) as planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine was documented on the Vaccine Administration screen of the eCRF. The investigator documented whether the decision to discontinue further vaccination/treatment was made by the subject's parents/ LARs or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-SAE.
- Other

## 5.4. Composition and administration of vaccines (Investigational Product)

### 5.4.1. Description of vaccines

Table 5 presents the formulation and presentation of study vaccines.

**Table 5 Study vaccines**

| Name of the Investigational Products: | liquid HRV vaccine | Placebo | DTPa | OPV |
|---|---|---|---|---|
| **Dosage form:** | Refer to Section 5.4.2 | Refer to Section 5.4.2 | Refer to Section 5.4.2 | Refer to Section 5.4.2 |
| **Source:** | RIX4414 HRV strain at least $10^{6.0}$ median $CCID_{50}$ Di-sodium Adipate 132.74 mg DMEM 2.26 mg Sucrose 48.8% (w/w) water for injection q.s. as 1.5 mL | Di-sodium Adipate 132.74 mg DMEM 2.26 mg Sucrose 48.8% (w/w) water for injection q.s. as 1.5 mL | Diphtheria toxoid ≥ 30 international units (IU) 25 Limits of flocculation (Lf) Tetanus toxoid ≥ 40 IU (10Lf) Pertussis toxoid 25 µg Filamentous haemagglutinin 25 µg Pertactin 8 µg Aluminium as salts 0.5 mg 2-phenoxyethanol ≤ 2.5 mg | per 0.1ml(2 drops) Total polio-virus, not less than 6.15lgCCID50 type1, not less than 6.0 lgCCID50 type2, not less than 5.0 lgCCID50 type3, not less than 5.5 lgCCID50 |
| **Lot number (BatchNumber)** | AROLA219B | PROLA008A | YC14B113AA | [20100202] |
| **Presentation (Specification)** | Liquid in a pre-filled oral applicator | Liquid in a pre-filled oral applicator | Turbid white suspension in a pre-filled syringe | liquid, oral |
| **Expiry date(Valid period)** | 30 September, 2012 | 31 October 2012 | 01 July,2012 | 01 February,2012 |

**Storage conditions:** Study vaccines were stored at the defined temperature range (i.e. +2 to +8°C). The storage temperature of the study vaccines was to be monitored daily while using validated temperature monitoring devices and the temperature measurements were to be recorded during working days, preferably at the same time of the day (e.g. at the beginning of the day). Freezing indication was to be continuously controlled by an appropriate device placed close to the study vaccines.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C), was to be reported to the Sponsor (i.e. Clinical Supplies Unit) as soon as detected. In case of temperature deviation between 0 and +2°C, the impacted study vaccines can still be administered, but the site must take adequate actions to go back to defined range +2 to +8°C and avoid re-occurrence of such a temperature deviation.

The liquid HRV vaccine and placebo used in this study were developed and manufactured by GSK Biologicals.

The DTPa vaccine used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 was developed and manufactured by GSK Biologicals.

The OPV vaccine used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 was developed and manufactured by Institute of Medical Biology Chinese Academy of Medical Sciences.

The Quality Control Standards and Requirements for the liquid HRV vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals were obtained.

The vaccines were labelled and packed according to applicable regulatory requirements.

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

### 5.4.2. Dosage and administration including administration route and basis for determining the administration route of study vaccines

The pre-filled oral applicator was shaken well before use. The product (vaccine or placebo) was then administered smoothly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration occurred in a quiet environment. Sufficient time was allowed for the baby to swallow the liquid vaccine solution, to avoid regurgitation or vomiting. If the subject regurgitated or vomited after study vaccine administration, no new study vaccine dose was administered. The subject continued to participate in the study. The oral vaccine intake characteristics (smooth vaccine intake, vaccine intake interrupted due to coughing or choking, regurgitation after vaccine intake, vomiting after vaccine intake) were recorded in the eCRF.

The vaccination regimen is summarised in Table 6.

**Table 6 Dosage and administration**

| Type of contact and time-point | Doses | Treatment Group | Vaccine | Route [1] | Site [2] | Side [3] |
|---|---|---|---|---|---|---|
| Visit 1 (day 0); Visit 2 (month 1) | 1 | Group HRV vaccine | liquid HRV vaccine | O | | |
| Visit 1 (day 0); Visit 2 (month 1) | 1 | Group Placebo | Placebo | O | | |
| Visit 2 (month 1); Visit 3 (month 2); Visit 4 (month 3) | 1 | Group HRV vaccine<br>Group Placebo | DTPa | IM | Ant T | L |
| Visit 1 (day 0); Visit 2 (month 1); Visit 3 (month 2) | 1 | Group HRV vaccine<br>Group Placebo | OPV | O | | |

[1]Oral (O)/ Intramuscular (IM)
[2]Thigh (T): Anterolateral (Ant)
[3]Left (L)

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

### 5.4.3. Treatment allocation and randomisation

The treatment allocation at the investigator site was performed using SBIR. The treatment numbers were allocated by kit. The randomisation algorithm used a minimisation procedure accounting for centre.

When SBIR was not available, SBIR user guide or the Study Procedures Manual (SPM) for specific instructions was used for reference.

After the eligibility of the subject was checked and ICF obtained, the site staff in charge of the vaccination accessed SBIR. Upon providing the subject identification number, the randomisation system used the minimisation algorithm to determine the treatment number to be used for the subject. Each treatment number was recorded in the eCRF on the Vaccine Administration screen.

#### 5.4.3.1. Randomisation of supplies

The randomisation was performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, a 6%-over-randomisation of supplies was prepared.

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

### 5.4.4. Randomisation of subjects to assay sub-cohorts

Randomisation for all the sub-cohorts was done in parallel. Blood samples were collected from both the sub-cohorts of subjects:

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).
- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300).

### 5.4.5. Blinding

The study was conducted in a double-blind manner with respect to the liquid HRV vaccine and placebo. The parents/LARs of the subjects, the study personnel and the investigator were unaware of the study vaccine administered (liquid HRV vaccine/Placebo).

The level of blinding was maintained throughout the conduct of the trial, and only when the data was cleaned to an acceptable level of quality, appropriate personnel were unblinded or required in case of a SAE.

The final analysis was done by GSK.

## 5.5. Prior and concomitant medication /vaccinations

At each study visit/contact, the investigator questioned the subject's parents/LARs about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, were recorded in the eCRF. This also applied to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

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 was considered to be prophylactic when it was given in the absence of fever and any other symptom, to prevent fever from occurring (Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.).

Similarly, concomitant medication administered for the treatment of a SAE, at any time, was recorded on the SAE screens in the eCRF.

## 5.6. Laboratory assays and time points (Observational index and observational list for Laboratory testing)

**GE Stool analysis**

All stool sample assays were performed at the GSK Biologicals designated Clearstone laboratory (China) using standardised, validated procedures. All GE stool samples were analysed by Enzyme Linked Immunosorbent Assay (ELISA) for detection of RV antigen. If a stool sample tested positive for RV antigen, the sample was tested by Polymerase Chain Reaction (PCR) to determine the G and P genotype. If any RV G1 strain was detected in the stool specimens from Visit 1 up to study end, viral strain of the vaccine was differentiated from the wild type strain by sequence analysis or an equivalent approach.

**Serum analysis**

All serum sample assays were performed at GSK Biologicals designated NIFDC laboratory (China) using standardised, validated procedures. The back-up serum samples are stored at GSK Biologicals designated Clearstone laboratory (China). Serum anti-rotavirus IgA antibody concentrations were to be measured in all serum samples collected at Visit 1, Visit 3 and Visit 6 using ELISA. The assay cut-off was 20 U/mL. Antibodies to all antigens contained in the co-administered vaccines were to be measured at Visit 1 and Visit 5 (applicable only for subjects in the immunogenicity sub-cohort 2).

The laboratory assays to be performed are presented in Table 7.

**Table 7 Laboratory Assays**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | GSK Biologicals* |
| Serum | anti-diphtheria | ELISA** | NIFDC | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-tetanus | ELISA** | NIFDC | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-PT | ELISA** | NIFDC | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-FHA | ELISA** | NIFDC | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-PRN | ELISA** | NIFDC | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | GSK Biologicals* |

*GSK Biologicals laboratory or validated laboratory (NIFDC ) designated by GSK Biologicals in China.
**or Multiplex
ELISA = Enzyme Linked Immunosorbent Assay
NIFDC = National Institute for Food and Drug Control
U = Units; IU = International Units; EL.U = Elisa Units
†$ED_{50}$ = Estimated dose 50% is the seroprotective level.

Collected samples were to be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

## 5.7. Assessment of efficacy variables (Observational index and observational list for Laboratory testing)

Parents/LARs of all subjects were instructed to collect a stool sample from the subject if the subject developed GE symptoms (defined as diarrhoea with or without vomiting) during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks). A GE stool sample was to be collected as soon as possible after the illness began. A second GE stool sample was to be collected if the first sample was insufficient. A stool sample was collected for each GE episode. Two occurrences of diarrhoea were classified as separate episodes if there was a five day or more diarrhoea-free days between the episodes.

For each suspected GE episode that occurred during the study period, a GE diary card was completed by the parents/LARs daily until end of the GE symptoms. The completed diary cards were returned to the investigator at the following study visit. The investigator verified the returned completed GE diary cards and he/she or the study personnel transcribed the information into the appropriate sections of the eCRF, in English.

## Assessment of GE episodes

Any GE episode (defined as diarrhoea with or without vomiting) that occurred starting from Visit 1 to study end was documented using the GE diary card. The following information was collected on the GE diary card during each GE episode: Axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given. The information collected on the GE diary card allowed the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

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

In the 20-point scoring system, points were assigned at GSK Biologicals according to the duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalisation (hospitalised subjects were considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 8.

**Table 8 The 20-point scoring system to determine the intensity of GE episodes reported during the study**

| Adverse Experience | Points |
|---|---|
| Duration of looser than normal stools (days) | |
| 1-4 | 1 |
| 5 | 2 |
| ≥ 6 | 3 |
| Maximum number of looser than normal stools /24 hours | |
| 1-3 | 1 |
| 4-5 | 2 |
| ≥ 6 | 3 |
| Duration of vomiting (days) | |
| 1 | 1 |
| 2 | 2 |
| ≥ 3 | 3 |
| Maximum number of episodes of vomiting/24 hours | |
| 1 | 1 |
| 2-4 | 2 |
| ≥ 5 | 3 |
| Fever∗<br>Axillary | |
| 36.6 – 37.9°C | 1 |
| 38.0 – 38.4°C | 2 |
| ≥ 38.5°C | 3 |
| Dehydration | |
| 1-5% | 2 |
| ≥ 6% | 3 |
| Treatment | |
| Rehydration | 1 |
| Hospitalisation | 2 |

∗The highest temperature recorded during the episode was scored.

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

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

## 5.8. Assessment of safety variables (Observational index and observational list for Symptoms and Signs)

### 5.8.1. Adverse events

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

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

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) were recorded in the medical history section of the subject's eCRF.

As a consistent method of soliciting AEs, the subject's parents/LARs were asked a non-leading question such as:

'*Did your child act differently or felt different in any way since receiving the vaccine or since the last visit?*'

When an AE/SAE occurred, it was the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator then recorded all relevant information regarding an AE/SAE on the eCRF or SAE Report screens as applicable. It was not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there could have been instances when copies of medical records for certain cases were requested by GSK Biologicals. In these instances, all subject identifiers were blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator attempted to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was documented as the AE/SAE and not the individual signs/symptoms.

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that were judged by the investigator to be

clinically significant were recorded as AEs or SAEs if they met the definition of an AE, or of a SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that were present or detected at the start of the study and did not worsen, were not reported as AEs or SAEs.

The investigator exercised his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

#### *5.8.1.1.1. Assessment of intensity*

Intensity of the following AEs was assessed as described in Table 9:

**Table 9 Intensity scales for solicited symptoms reported during the solicited follow-up period**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Fever* | | Recorded temperature in °C |
| Irritability/Fussiness | 0 | Behaviour was as usual |
| | 1 | Mild: Cried more than usual/no effect on normal activity |
| | 2 | Moderate: Cried more than usual/interfered with normal activity |
| | 3 | Severe: Crying that could not be comforted/prevented normal activity |
| Diarrhoea¶ | | Recorded the number of looser than normal stools /day |
| Vomiting§ | | Recorded the number of vomiting episodes/day |
| Loss of appetite | 0 | Appetite was as usual |
| | 1 | Mild: Ate lesser than usual/no effect on normal activity |
| | 2 | Moderate: Ate lesser than usual/interfered with normal activity |
| | 3 | Severe: Did not eat at all |
| Cough/runny nose | 0 | Normal |
| | 1 | Mild: Coughed/runny nose which was easily tolerated |
| | 2 | Moderate: Coughed/runny nose which interfered with daily activity |
| | 3 | Severe: Coughed/runny nose which prevented daily activity |
| Drowsiness | 0 | Behaviour was as usual |
| | 1 | Mild: Drowsiness was easily tolerated |
| | 2 | Moderate: Drowsiness that interfered with normal activity |
| | 3 | Severe: Drowsiness that prevented normal activity |
| Gastrointestinal symptoms (nausea,vomiting, diarrhoea and/or abdominal pain) | 0 | Gastrointestinal symptoms were normal |
| | 1 | Mild: Gastrointestinal symptoms that were easily tolerated |
| | 2 | Moderate: Gastrointestinal symptoms that interfered with normal activity |
| | 3 | Severe: Gastrointestinal symptoms that prevented normal activity |

*Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities
¶Diarrhoea was defined as passage of three or more, looser than normal stools within a day.
§Vomiting was defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day

**Table 10 Intensity scales used for diarrhoea, vomiting and fever reported during the solicited follow-up period**

| Adverse Experience | Intensity grade | Parameter |
|---|---|---|
| Diarrhoea | 0 | Normal (0 - 2 looser than normal stools/day) |
| | 1 | 3 looser than normal stools/day |
| | 2 | 4 - 5 looser than normal stools/day |
| | 3 | ≥ 6 looser than normal stools/day |
| Vomiting | 0 | Normal (no emesis) |
| | 1 | 1 episode of vomiting/day |
| | 2 | 2 episodes of vomiting/day |
| | 3 | ≥ 3 episodes of vomiting/day |
| Fever* | 0 | Axillary temperature < 37.1 °C |
| | 1 | Axillary temperature 37.1 °C - 37.5 °C |
| | 2 | Axillary temperature 37.6 °C - 39.0 °C |
| | 3 | Axillary temperature > 39.0 °C |
| Fever** | 0 | Axillary temperature < 37.5°C |
| | 1 | Axillary temperature ≥ 37.5 – ≤ 38.0°C |
| | 2 | Axillary temperature > 38.0 – ≤ 39.0°C |
| | 3 | Axillary temperature > 39.0°C |

*The maximum intensity of fever using the grading scale as defined by Chinese authorities.
**The maximum intensity of fever using the grading scale as defined by GSK Biologicals.

Intensity of the following solicited local AEs (DTPa vaccine) was assessed as described in Table 11.

**Table 11 Intensity scales for solicited local symptoms**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Pain at injection site | 0 | None |
| | 1 | Mild: Minor reaction to touch |
| | 2 | Moderate: Cried/protested on touch |
| | 3 | Severe: Cried when limb was moved/spontaneously painful |
| Redness at injection site | | Recorded greatest surface diameter in mm |
| Swelling at injection site | | Recorded greatest surface diameter in mm |

The maximum intensity of local injection site redness/swelling was scored at GSK Biologicals using the guidelines of AE grading set by Chinese Vaccine Clinical Research Guidelines as follows:

**Table 12 Intensity grades for redness/swelling**

| Intensity grade | Parameter |
|---|---|
| 0 | Absent |
| 1 | < 15 mm |
| 2 | ≥ 15 mm and ≤ 30 mm |
| 3 | > 30 mm |

The investigator assessed the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment was based on the investigator's clinical judgement.

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

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

An AE that was assessed as Grade 3 (severe) was not to be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs were assessed as Grade 3. An event was defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 5.8.2.

#### *5.8.1.1.2. Assessment of causality*

The investigator was obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator used clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product were considered and investigated. The investigator also consulted the Investigator Brochure in the determination of his/her assessment.

There could have been situations when a SAE had occurred and the investigator had minimal information to include in the initial report to GSK Biologicals. However, it was very important that the investigator always made an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator could change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment was one of the criteria used when determining regulatory reporting requirements.

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

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

*Was there a reasonable possibility that the AE may have been caused by the liquid HRV vaccine?*

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

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

Non-serious and serious AEs were evaluated as two distinct events. If an event met criteria to be determined 'serious' (see Section 5.8.2 for definition of SAE), additional examinations/tests were performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors included:

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

#### *5.8.1.1.3. Assessment of outcomes*

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study was assessed as:

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

### 5.8.2. Serious adverse events

#### 5.8.2.1. Definition of a serious adverse event

A SAE was any untoward medical occurrence that:

a. resulted in death.

b. was life-threatening.

NB: 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 could have caused death, had it been more severe.

c. Required hospitalisation or prolongation of existing hospitalisation.

NB: In general, hospitalisation signified that the subject had been admitted 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 also considered AEs. If a complication prolonged hospitalisation or fulfilled any other serious criteria, the event was considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE was considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline was NOT considered an AE.

d. Resulted in disability/incapacity,

NB: 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 like illness, and accidental trauma (e.g. sprained ankle) which could have interfered or prevented everyday life functions but did not constitute a substantial disruption.

Medical or scientific judgement was exercised in deciding whether reporting was appropriate in other situations, such as important medical events that were not immediately life-threatening or resulted in death or hospitalisation but could have jeopardised the subject or could have require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalisation.

## 5.9. Statistical methods (Statistical Processing Scheme)

The statistical analyses were performed using the SDD (i.e **S**AS **D**rug and **D**evelopment) web portal version 3.5 and SAS version Proc stat xact 8.1.

The study endpoints considered for analyses presented in this study report are listed below. Immunogenicity endpoints will be presented in a separate annex report.

### 5.9.1. Primary outcome/Efficacy Variable

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

### 5.9.2. Secondary Outcome/Efficacy Variables

***Efficacy***

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

***Reactogenicity and Safety***

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

### 5.9.3. Determination of sample size

Target enrolment was 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated rate of non evaluable subjects was 20%.

Considering a 1:1 randomisation ratio and various incidence rates, Table 13 provides the power to observe a lower limit of the 95% CI for vaccine efficacy to be above 0% and 10%.

For a 2% attack rate of RV GE in the placebo group from 2 weeks post Dose 2 to end of efficacy follow-up period, and if the vaccine efficacy was 80%, the study had 95.8% power to observe a 95% CI for the vaccine efficacy that could be above 10%. It was expected to observe a total of 40 severe RV GE cases during the efficacy follow-up period in the total vaccinated cohort.

**Table 13 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 2600 evaluable subjects – 1300 subjects in HRV group and 1300 subject in the placebo group, power based on 1,000 simulations using Proc StatXact)**

| Incidence rate in the Placebo for severe RV GE | VE (%) | Power to have a lower limit of the 95%CI on VE ≥ 0% | Power to have a lower limit of the 95%CI on VE ≥ 10% |
|---|---|---|---|
| 1% | 70 | 54.5% | 44.2% |
| | 80 | 69.6% | 60.8% |
| 1.5% | 70 | 74.4% | 65.1% |
| | 80 | 87.8% | 82.7% |
| 2%* | 70 | 85.1% | 77.2% |
| | 80** | 97.6% | 95.8% |
| 2.5% | 70 | 92.7% | 87.8% |
| | 80 | 99.4% | 98.6% |
| 3% | 70 | 96.4% | 92.3% |
| | 80 | 99.4% | 99.3% |

*anticipated rate in the Placebo for severe RV GE.
VE - Vaccine Efficacy. CI-Confidence Interval
**anticipated vaccine efficacy
Attack Rate (AR) = 1.5% [1.0%; 2.3%], VE = 95.3% [73.1%;99.9%].

### 5.9.4. Study cohorts /data sets analyzed

#### 5.9.4.1. Total vaccinated cohort

The total vaccinated cohort included all subjects with at least one dose of the liquid HRV vaccine or placebo administration documented:

- A safety analysis based on the total vaccinated cohort included all vaccinated subjects,
- An efficacy analysis based on the total vaccinated cohort included all vaccinated subjects for whom efficacy follow-up data was available.

#### 5.9.4.2. ATP cohort for analysis of safety

The ATP cohort for safety included all vaccinated subjects:

- who received at least one dose of HRV vaccine/Placebo according to their random assignment.
- for whom the randomisation code was not broken, who did not received a vaccine forbidden by or not specified in the protocol.

#### 5.9.4.3. ATP cohort for analysis of efficacy

The ATP cohort for efficacy included all subjects from ATP the cohort for safety.

- 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 received 2 doses of the liquid HRV vaccine or placebo,
- who have entered the efficacy surveillance period:
  - have follow-up beyond 2 weeks post Dose 2 of study vaccination
  - who have no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks post Dose 2 of liquid HRV vaccine or placebo.

## 5.10. According-to-protocol cohort for analysis of efficacy for second year follow-up

- The ATP cohort for efficacy for second year follow-up will include all subjects from ATP cohort for efficacy, who have follow-up beyond visit 6 (year 1).

### 5.10.1. Derived and transformed data

**Demography**

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

**Efficacy**

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

The subjects, who had completed Visit 6 and had not given their consent to participate in the extension follow-up, were considered as dropouts from the study. The ATP cohort for the analysis of efficacy included all the subjects who had satisfied the points mentioned in the section 5.9.4.3.

**Safety/Reactogenicity**

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

### 5.10.2. Analysis of demographics (Analysis)

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 were calculated per group and overall. The racial and gender composition was presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall. The distribution of subjects enrolled among the study centres was tabulated as a whole and per group. The percentages of subjects who received concomitant and intercurrent vaccinations were tabulated by group.

### 5.10.3. Analysis of efficacy (Analysis)

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

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

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

- any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to each non-G1 type during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe all cause GE during the efficacy follow-up period.

Vaccine efficacy was also derived from a Cox regression model on the time to first event with censoring for subjects without an event as an additional supportive and exploratory analysis.

Vaccine efficacy analysis was also performed on the data collected from 2 weeks post Dose 2 of HRV vaccine /placebo up to visit 6. This was presented as an additional supportive analysis.

- The primary objective was considered met if the lower limit of the 95% confidence interval on vaccine efficacy (conditional method) for the HRV group against severe RVGE caused wild-type RV strains during the efficacy follow-up period was ≥ 10.

Vaccine efficacy, derived from a Cox regression model on the time to first event with censoring at the database lock for subjects without event. The model included the group as fixed effect. This was performed as an exploratory/supportive analysis. [Kalbfleisch, 2002]

- Incidence rate in a group (P) was computed as the number of subjects reporting at least one event (n)/total follow-up time to a first event censored at visit 7 (T). The associated 95% CI's were obtained considering that n follows a Poisson distribution with P*T parameter.
- The number of events prevented by 100 vaccinated infant-years was obtained from 100 times the difference in the incidence rate. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008]. This was performed as an exploratory/supportive analysis.
- An exploratory/supportive analysis of vaccine efficacy by serostatus of subjects against rota virus IgA antibody at Visit 3 will be performed.

The same analysis was also performed on Total Vaccinated Cohort from Dose 1 to study end and from Dose 1 to Visit 6.

An exploratory analysis of efficacy was performed on the efficacy data collected between Visit 6 to visit 7 on the subjects who have follow-up beyond Visit 6 (ATP cohort for efficacy for second year follow-up).

### 5.10.3.1. Analysis of Safety (Analysis)

***Analysis of Safety (solicited AEs):***

The analysis of safety was based on the TVC. As the percentage of enrolled subjects excluded from the ATP cohort for safety was lower than 5% in both groups, no analysis based on the ATP cohort was performed.

Note: Intensity of fever was assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale was performed separately.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each dose, for overall doses and per subject. The same calculations will be performed for any grade 3 (solicited or unsolicited) symptoms and for any (solicited or unsolicited) symptom related to vaccination.

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

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects with at least one local AE (solicited and unsolicited) after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination were tabulated with exact 95% CI. The same calculations were performed for any grade 3 (solicited or unsolicited) symptoms, grade 3 related symptoms and for any symptoms requiring medical attention.

- The percentage of subjects reporting each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa during the 8-day (Days 0–7) follow-up period with exact 95% CI were tabulated.

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation were done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

**For all subjects:**

The incidence, with exact 95% CI, of each individual solicited general symptom common to both the sub-cohorts, will be calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

- Occurrence of fever was reported per 0.5°C cumulative temperature increments

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

SAEs reported during the study period (i.e. from first vaccine dose till study end) were described in detail.

There was a retrospective follow-up on SAEs for subjects who had already completed Visit 6 prior to the implementation of protocol amendment 2 and this was documented in the eCRF.

### 5.10.4. Sequence of analyses

Final analysis was to be done as per protocol, when 40 severe RV GE episodes caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or at study conclusion, whichever was the earliest. Interim analysis

No interim analysis was planned for this study.

## 5.11. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, electronic case report form and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the Company representative(s) prior to study start. An investigator meeting was held prior to the study start.

**Independent Audit statement:**

- This study was subject to audit by GSK's Clinical Development Quality Assurance (CDQA) at the centre number 81519, on 26$^{th}$-27$^{th}$ June 2010.

## 5.12. Changes in the conduct of the study or planned analyses (Modification in process of study)

### 5.12.1. Protocol amendments

**Protocol Amendment 1 (02 September 2010):**

The following changes were reflected in Protocol amendment 1: 6% over-randomisation of supplies, parallel randomisation of subjects to assay sub-cohorts and change in time periods for administration of medications/products that could have led to the elimination of a subject from ATP analyses.

**Protocol Amendment 2 (05 August 2011):**

The protocol was amended again on 05 August 2011 to reflect the extension of the efficacy follow-up period until the end of the second RV season in China. Based on the preliminary review of GE episodes reported prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seemed lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up was extended until approximately April 2012 (i.e. end of RV season in China).

### 5.12.2. Other changes

This study was conducted according to the protocol.

Analyses were performed as planned in the protocol and/or SAP except for the following changes:

- The cohort "ATP cohort for efficacy – Extended follow-up" will be referred to as "ATP cohort for efficacy for second year follow up" in the report tables.
- Table for VE by RV types was generated for the data between Visit 6 & Visit 7 on ATP cohort for efficacy for second year follow up.
- Tables on all cause of GE, Severe GE & Hospitalized due to RVGE was generated for Dose 1 up to before Dose 2 and Dose 1 up to 2 weeks post-Dose 2 on TVC.
- Table for concomitant medication was generated on sub-cohort 2 from Day 0 to Day 7 and on pooled sub-cohorts for entire study period.
- Percentage of subjects reporting unsolicited symptoms during the entire study period was generated on TVC.
- Titles for some of the tables was changed from "subjects belonging to sub cohort 1 and 3" to "except immunogenicity sub cohort 2" and from "subjects belonging to immunogenicity sub cohort 2" to "except immunogenicity sub cohorts".

This report presents the efficacy, safety and reactogenicity results of the subjects after study completion. Immunogenicity results are not yet available and will be presented in an annex report.

- The final analysis presents the efficacy, safety and reactogenicity data collected from Dose 1 of HRV/Placebo up to Visit 7 and this analysis was run by a GSK statistician. All individual data listings except for immunogenicity data are presented along with this reported.
- An annex report will present the immunogenicity data collected during the study. This analysis will present the individual data listings for immunogenicity data.

# 6. STUDY POPULATION RESULTS (STUDY RESULTS)

## 6.1. Study dates

The first subject was enrolled in the study on 29 August 2010 and the last study visit was on 12 May 2012.

## 6.2. Subject eligibility and attrition from the study

### 6.2.1. Number of subjects

The number of subjects enrolled in the study by centre is presented in the following tables:

Table 14 Number of subjects by centre (Total vaccinated cohort)

Table 15 Subjects unblinded before database lock (13AUG2012) (Total vaccinated cohort)

Table 16 Number of subjects in the sub-cohorts (Total vaccinated cohort)

### 6.2.2. Study completion and withdrawal from study

The reasons for withdrawal are presented in the following table:

Table 17 Number of subjects entered, completed and withdrawn with reason for withdrawal till Visit 7 (Total vaccinated cohort)

### 6.2.3. Protocol deviations

The deviations are presented in the following table:

Table 18 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

Table 19 Protocol deviations not leading to exclusion of subjects or their data from analysis

## 6.3. Demographic characteristics

### 6.3.1. ATP cohort for efficacy

The demographic characteristics and the vital signs are presented in the following tables:



### 6.3.2. Total Vaccinated cohort

The demographic characteristics are presented in the following table:



## 6.4. Concomitant and Intercurrent Vaccinations

The summary of co-administered vaccines and vaccinations other than the investigational product are presented in the following tables:

# 7. EFFICACY RESULTS

## 7.1. Data sets analyzed

Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) and the total vaccinated cohort. See Section 5.9.4 for the definition of the cohorts identified for analyses and Section 6.2 eligibility for analyses.

## 7.2. According-to-protocol analysis for efficacy

### 7.2.1. Characterization of GE episodes

The results are detailed in the following tables and figures:



- A total of 728 subjects (46.2%) from the HRV group and 759 subjects (48.3%) from the placebo group had reported at least one GE episode (Table 36).
- Of all the GE episodes that were tested, rotavirus was detected in 70 GE episodes (4.4%) in the HRV group and 167 GE episodes (10.6%) in the placebo group (Table 36).
- Severe RV GE was reported for 21 subjects (1.3%) and for 75 subjects (4.8%) in the HRV group and placebo group, respectively (Table 36).

- When the GE and RV GE episodes were scored using the 20-point Vesikari scale, the distribution of the reported GE episodes among mild, moderate and severe intensity was similar in both groups. There were more RV GE episodes rated as severe (Vesikari scale ≥11) in the placebo group [75 RV GE episodes (44.1%) as compared to 21 (30%) RV GE episodes in the HRV group] (Table 37).

The percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 39 Percentage of subjects with RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

Table 40 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 41 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

Table 42 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

- Among the RV GE episodes, G1P[8] (27.1% in the HRV group and 20.0% in the placebo group) and G2P[4] (55.7% in the HRV group and 57.0% in the placebo group) were the most common RV types circulating during the efficacy period (Table 41).
- Among the severe RV GE episodes, G1P[8] (38.1% in the HRV group and 24.0% in the placebo group) and G2P[4] (47.6% in the HRV group and 49.3% in the placebo group) were the most common RV types circulating during the efficacy follow-up period (Table 42).

Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:

Table 43 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 44 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G1WT type (ATP cohort for efficacy)

Table 45 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G2 type (ATP cohort for efficacy)

In general, clinical RV GE episodes were more severe (based on Vesikari scale) and had longer duration of symptoms in the placebo group when compared to the HRV group (Table 43 to Table 49).

The duration of efficacy follow-up is presented in the following table and figures:



- The mean duration of efficacy follow-up from 2 weeks post Dose 2 up to Visit 7 was 1.34 years in the HRV group and 1.33 years for the placebo group.

### 7.2.2. Vaccine efficacy from 2 weeks after Dose 2 up to Visit 7

#### 7.2.2.1. Vaccine efficacy against severe RV GE (Primary Endpoint)

The results are detailed in the following tables and figures:

Table 51 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 52 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Figure 4 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV was 72.0% [95% CI: 54.1%; 83.6%]. Severe RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (1.3% versus 4.8%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 51). The primary objective of the study was met since the lower limit of the 95% CI on VE was above 10% (pre-specified criteria for the primary efficacy objective).
- Vaccine efficacy based on Cox proportional hazard model against severe RV GE was 72.7% [95% CI: 55.8%; 83.2%]. Per 100 infant years, 2.7 episodes of severe RV GE can be prevented if the subjects are vaccinated with the liquid HRV vaccine (Table 58 and Table 59).

#### 7.2.2.2. Vaccine efficacy against any RV GE

The results are detailed in the following table and figure:

Table 53 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Figure 5 The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.1% [95% CI: 44.3%; 68.8%]. RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (4.4% versus 10.6%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 53).

- Vaccine efficacy based on Cox proportional hazard model against RV GE was 60% [95% CI: 47.1%; 69.7%]. Per 100 infant years, 5.1 episodes of any RV GE could be

prevented by vaccinating the subjects with the liquid HRV vaccine (Table 58 and Table 59).

#### 7.2.2.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figures:

Table 54 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)

Table 55 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)

Figure 6 The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Figure 7 The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against severe RV GE caused by G1 and non-G1 RV GE strains was 64.0% [95% CI: 20.4%; 85.2%] and 77.8% [95% CI: 58.0%; 89.2%], respectively (Table 54).
- Vaccine efficacy against severe RV GE caused by wild type G1P[8] was 60.1% [95% CI: 5.3%; 84.8% ]. Among the subjects reported for severe RV GE episodes, wild type G1P[8] was identified for 0.5% subjects in the HRV group and 1.3% subjects in the placebo group (Table 55).
- Vaccine efficacy against severe RV GE caused by G2P[4] was 72.5% [95% CI: 45.5%; 87.3%]. Among the subjects reported for severe RV GE episodes, G2P[4] was identified for 0.7% subjects in the HRV group and 2.5% subjects in the placebo group (Table 55).

**Vaccine efficacy against any RV GE by RV type**

Table 56 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)

Table 57 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)

Table 58 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against any RV GE caused by wild type G1P[8] was 47.4% [95% CI: 7.4%; 71%]. Among the subjects reported for any RV GE episodes caused by G1 types, wild type G1P[8] was identified for 1.3% subjects in the HRV group and 2.4% subjects in the placebo group (Table 57).
- Vaccine efficacy against any RV GE caused by G2P[4] was 58.9% [95% CI: 40.5%; 72.0%]. Among the subjects reported for any RV GE episodes caused by non-G1 types, G2P[4] was identified for 2.7% subjects in the HRV group and 6.5% subjects in the placebo group (Table 57).

#### 7.2.2.4. Vaccine efficacy against hospitalisation due to RV GE



- Vaccine efficacy against RV GE caused by circulating wild-type RV that required hospitalization was 81.0% [95% CI: 43.6%; 95.3%]. Fewer subjects in the HRV group required hospitalization following an episode of RV GE as compared to the placebo group (0.3% versus 1.3%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 60).
- Vaccine efficacy against RV GE leading to hospitalization or requiring rehydration therapy was 66.4% [95% CI: 49.6%; 78.1%]. Fewer subjects in the HRV group were hospitalized and/or required rehydration therapy following an episode of RV GE as compared to the placebo group (2.1% versus 6.2%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 61).

#### 7.2.2.5. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 62 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 63 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 64 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 65 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against all cause GE was 4.2% [95% CI: -6.2%; 13.6%]. All cause GE episodes occurred at a similar rate in the HRV group and placebo group (46.2% versus 48.3%, p-value 0.422) from 2 weeks post Dose 2 up to the Visit 7 (Table 62).
- Vaccine efficacy against all cause severe GE was 9.3% [95% CI: -11.1%; 26.0%]. All cause severe GE episodes occurred at a similar rate in the HRV group and placebo group (11.9% versus 13.1%, p-value: 0.357) from 2 weeks post Dose 2 up to the Visit 7 (Table 63).
- Vaccine efficacy against all cause GE that required hospitalization was 41.2% [95% CI: 13.1%; 60.6%]. Fewer subjects in the HRV group required hospitalization following an episode of all cause GE as compared to the placebo group (2.7% versus 4.6%, p-value 0.007) from 2 weeks post Dose 2 up to the Visit 7 (Table 64).

### 7.2.3. Vaccine efficacy results from 2 weeks after Dose 2 up to Visit 6

The results are detailed in the following tables and figures:

Table 66 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 67 Number of GE episodes reported from 2 weeks after Dose 2 up to Visit 6 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

Table 68 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

The percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

The number of RV GE and severe RV GE episodes by G P type are presented in the following tables:



Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:



The duration of efficacy follow-up is presented in the following table and figures:

#### 7.2.3.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables and figures:



#### 7.2.3.2. Vaccine efficacy against any RV GE

The results are detailed in the following table and figure:



- Fewer subjects in the HRV group reported any RV GE episode caused by the circulating wild-type RV compared to the placebo group (1.7% versus 5.7%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 6.
- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 70% [95% CI: 53.5%; 81.3%] (Table 82).

#### 7.2.3.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figure:

**Vaccine efficacy against any RV GE by RV type**

The results are detailed in the following tables and figures:



#### 7.2.3.4. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:

### 7.2.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 91 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 92 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 93 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 94 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

### 7.2.5. Characterization of GE episodes after Visit 6 up to Visit 7

The results are detailed in the following tables:

Table 95 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

Table 96 Number of GE episodes reported from Visit 6 up to Visit 7 by severity using the 20-point Vesikari scale (ATP cohort for efficacy - second year follow-up period)

Table 97 Percentage of GE episodes with no available stool results from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 98 Percentage of subjects with RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

Table 99 Percentage of subjects with severe RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 100 Number of RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

Table 101 Number of severe RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

The duration of efficacy follow-up is presented in the following table:

Table 102 Duration (in years) of efficacy follow-up period - from Visit 6 up to Visit 7 (ATP cohort for efficacy - second year follow-up period)

## 7.2.6. Vaccine efficacy from after Visit 6 up to Visit 7

### 7.2.6.1. Vaccine efficacy against severe RV GE

The results are detailed in the following table:

Table 103 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

### 7.2.6.2. Vaccine efficacy against any RV GE

The results are detailed in the following table:

Table 104 Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following table:

Table 105 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)

**Vaccine efficacy against any RV GE by RV type**

The results are detailed in the following table:

Table 106 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)

#### 7.2.6.3. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:

Table 107 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

#### 7.2.6.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 108 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Visit 6 up to Visit 7

Table 109 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Visit 6 up to Visit 7

Table 110 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

## 7.3. Total vaccinated cohort analysis

### 7.3.1. Characterization of GE episodes from Dose 1 to Visit 7

The results are detailed in the following tables and figures:

Table 111 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 up to Visit 7 (Total vaccinated cohort)

Table 112 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to Visit 7 (Total vaccinated cohort)

Table 113 Number of GE episodes reported from Dose 1 up to Visit 7 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

Table 114 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 7 (Total vaccinated cohort)

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 115 Percentage of subjects with RV GE episodes from Dose 1 up to Visit 7 by G and P type (Total vaccinated cohort)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:



Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:



The duration of efficacy follow-up is presented in the following table and figures:

## 7.3.2. Vaccine efficacy during the period from Dose 1 up to Visit 7

### 7.3.2.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables and figures:

Table 127 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

Table 128 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

Figure 24 The Kaplan Meier curve for severe RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)

Figure 25 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from Dose 1 up to Visit 7 (Total vaccinated cohort)

### 7.3.2.2. Vaccine efficacy against any RV GE

The results are detailed in the following tables and figure:

Table 129 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

Figure 26 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)

### 7.3.2.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figures:

Table 130 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by RV type (Total vaccinated cohort)

Table 131 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by combination of G and P types (Total vaccinated cohort)

Figure 27 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 7 (Total vaccinated cohort)

**Vaccine efficacy against any RV GE by RV type**



#### 7.3.2.4. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:



#### 7.3.2.5. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

### 7.3.3. Characterization of GE episodes from Dose 1 up to Visit 6

The results are detailed in the following tables and figures:



Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:



The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:



Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:

The duration of efficacy follow-up is presented in the following table and figures:



### 7.3.4. Vaccine efficacy during the period from Dose 1 up to Visit 6

#### 7.3.4.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables and figures:

#### 7.3.4.2. Vaccine efficacy against any RV GE

The results are detailed in the following tables and figure:

Table 158 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

Figure 36 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 6 (Total vaccinated cohort)

#### 7.3.4.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figures:

Table 159 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)

Table 160 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)

**Vaccine efficacy against any RV GE by RV type**

Table 161 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)

Table 162 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)

Table 163 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from Dose 1 up to Visit 6 (Total vaccinated cohort)

Table 164 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 6 by Cox method (Total vaccinated cohort)

Figure 37 The Kaplan Meier curve for any RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)

Figure 38 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 6 (Total vaccinated cohort)

Figure 39 The Kaplan Meier curve for severe RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)

#### 7.3.4.4. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:



#### 7.3.4.5. Vaccine efficacy against all cause GE

The results are detailed in the following tables:



### 7.3.5. Characterization of GE episodes from Dose 1 up to before Dose 2

The results are detailed in the following tables:

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 174 Percentage of subjects with RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

Table 175 Percentage of subjects with severe RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

No record exists for the above mentioned table.

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 176 Number of RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

Table 177 Number of severe RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

No record exists for the above mentioned table.

The duration of efficacy follow-up is presented in the following table:

Table 178 Duration (in years) of efficacy follow-up period - Dose 1 up to before Dose 2 (Total vaccinated cohort)

## 7.3.6. Vaccine efficacy during the period from Dose 1 before Dose 2

### 7.3.6.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables:

Table 179 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

No record exists for the above mentioned table.

### 7.3.6.2. Vaccine efficacy against any RV GE

The results are detailed in the following table:

Table 180 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

#### 7.3.6.3. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following table:

Table 181 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

No record exists for the above mentioned table.

#### 7.3.6.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 182 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

Table 183 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

### 7.3.7. Characterization of GE episodes from Dose 1 up to 2 weeks post dose 2

The results are detailed in the following tables:

Table 184 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort )

Table 185 Number of GE episodes reported from Dose 1 up to 2 weeks post-Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

Table 186 Percentage of GE episodes with no available stool results from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 187 Percentage of subjects with RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

Table 188 Percentage of subjects with severe RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

Table 189 Number of RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 190 Number of severe RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

The duration of efficacy follow-up is presented in the following table:

Table 191 Duration (in years) of efficacy follow-up period from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

## 7.3.8. Vaccine efficacy during the period from Dose 1 up to 2 weeks post dose 2

### 7.3.8.1. Vaccine efficacy against severe RV GE

The results are detailed in the following table:

Table 192 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

### 7.3.8.2. Vaccine efficacy against any RV GE

The results are detailed in the following table:

Table 193 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

### 7.3.8.3. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following table:

Table 194 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

No record exists for the above mentioned table.

### 7.3.8.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 195 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

## 7.4. Efficacy summary

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV was 72.0% [95% CI: 54.1%; 83.6%]. Severe RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (1.3% versus 4.8%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7. The primary objective of the study was met since the lower limit of the 95% CI on vaccine efficacy was above 10% (pre-specified criteria for the primary efficacy objective).
- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.1% [95% CI: 44.3%; 68.8%]. RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (4.4% versus 10.6%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating wild type G1 was 52.2% [95% CI: 19.0%; 72.6%] and 64.0% [95% CI: 20.4%; 85.2%], respectively. Vaccine efficacy against severe RV GE caused by circulating wild type G1P[8] was 60.1% [95% CI: 5.3%; 84.8%]. Vaccine efficacy against any RV GE caused by G1P[8] was 47.4% [95% CI: 7.4%; 71%, p-value 0.024]. Fewer subjects in the HRV group reported any and severe RV GE caused by circulating wild-type G1 compared to the placebo group (1.4% and 0.6% versus 2.9% and 1.6% , respectively, p-value 0.005 and 0.009) from 2 weeks post-Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating non-G1 type was 62.1% [95% CI: 46.9%; 73.3%] and 77.8% [95% CI: 58.0%; 89.2%], respectively. Fewer subjects in the HRV group reported any and severe non-G1 type RV GE episode compared to the placebo group (3.1% and 0.8% versus 8.2% and 3.4%, respectively, p-value <0.001 for both) from 2 weeks post-Dose 2 up to the Visit 7. Vaccine efficacy against any RV GE caused by G2P[4] was 58.9% [95% CI: 40.5%; 72.0%, p-value <0.001].Vaccine efficacy against severe RV GE caused by G2P[4] was 72.5% [95% CI: 45.5%; 87.3%].
- Vaccine efficacy against RV GE caused by circulating wild-type RV that required hospitalization was 81% [95% CI: 43.6%; 95.3%]. Fewer subjects in the HRV group required hospitalization following an episode of RV GE as compared to the placebo group (0.3% versus 1.3%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against RV GE leading to hospitalization or requiring rehydration therapy was 66.4% [95% CI: 49.6%; 78.1%]. Fewer subjects in the HRV group were hospitalized and/or required rehydration therapy following an episode of RV GE as compared to the placebo group (2.1% versus 6.2%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.

- Vaccine efficacy against all cause GE was 4.2% [95% CI: -6.2%; 13.6%]. All cause GE episodes reported for subjects in HRV group and placebo group was similar (46.2% versus 48.3%, p-value 0.422) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause severe GE was 9.3% [95% CI: -11.1%; 26.0%]. All cause severe GE episodes for subjects in HRV group and placebo group was similar (11.92% versus 13.1%, p-value: 0.357) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause GE that required hospitalization was 41.2% [95% CI: 13.1%; 60.6%]. Fewer subjects in the HRV group required hospitalization following an episode of all cause GE as compared to the placebo group (2.7% versus 4.6%, p-value 0.007) from 2 weeks post Dose 2 up to the Visit 7.

# 8. SAFETY RESULTS

## 8.1. Data sets analyzed

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

## 8.2. Total vaccinated cohort analysis

The results are detailed in the following tables:

Table 197 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort)

Table 198 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort- except immunogenicity sub-cohorts)

Table 199 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort- Immunogenicity sub-cohort 2)

Table 200 Compliance in returning symptom sheets (Total vaccinated cohort- except immunogenicity sub cohort 2)

Table 201 Compliance in returning symptom sheets (Total vaccinated cohort- Immunogenicity sub cohort 2)

- The majority (at least 95.8%) of the subjects in the HRV group and placebo group received both doses (Table 197).
- Symptom sheets were completed for at least 98% of the doses in both groups (Table 200 and Table 201).

### 8.2.1. Overall incidence of adverse events

The results are detailed in the following tables:

All subjects except immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any AEs (solicited or unsolicited) based on GSK scale for fever (44.2% in the HRV group and 47.3% in the placebo group) and Chinese scale for fever (51.5% in the HRV group and 53.8% in the placebo group) was similar in both groups. There was no increase in the incidence of AEs (solicited or unsolicited) from Dose 1 to Dose 2 of the HRV vaccine (Table 202 and Table 203).
- The incidence of AEs (solicited or unsolicited) rated as grade "3" in intensity and those assessed as causally related to vaccination were also similar in both groups (Table 204 and Table 205).

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any general symptoms (solicited or unsolicited) was 52.9% [95% CI 44.7%; 61.1%] subjects in the HRV group and 50.3% [95% CI: 42.1%; 58.5%] subjects in the placebo group. Any general symptoms (solicited or unsolicited) were reported for 42.5% [95% CI: 34.5%; 50.7%] and 30.0% [95% CI: 22.8%; 38.0%] subjects after the first and second dose of HRV vaccine, respectively. No more than 16.0% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine (Table 207).
- During the 8-day follow-up period (Day 0 to Day 7), any general symptoms (solicited or unsolicited) rated as grade "3" in intensity and causally related to vaccination were reported for 2.6% [95% CI: 0.7%; 6.6%] subjects in the HRV group and 2.0% [95% CI: 0.4%; 5.6%] subjects in the placebo group. No more than 1.3% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine (Table 210).
- During the 8-day follow-up period (Day 0 to Day 7), any AEs (solicited or unsolicited) requiring medical attention were reported for 12.4% [95% CI: 7.6%; 18.7%] subjects in the HRV group and 11.1% [95% CI: 6.6%; 17.2%] subjects in the placebo group (Table 211).

### 8.2.2. Solicited local adverse events

All subjects in the immunogenicity sub-cohort 2:

The results are detailed in the following table:

Table 213 Percentage of subjects reporting each solicited local symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- Immunogenicity sub-cohort 2)

- During the 8-day (Day 0- Day 7) follow-up period, redness was the most frequently reported solicited local symptom for 13.3% subjects in the HRV group and 8.6% subjects in the placebo group. The most frequently reported grade "3" solicited local AEs were pain for 1.3% of subjects in the HRV group and redness for 0.7% of subjects in the placebo group. The solicited local symptoms were related to DTPa vaccine given intramuscularly (Table 213).

### 8.2.3. Solicited general adverse events

The results are detailed in the following tables:

Table 214 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort)

Table 215 Percentage of doses and subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

Table 216 Percentage of subjects reporting fever during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

Table 217 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

Table 218 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- except immunogenicity sub-cohort 2)

Table 219 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination

during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

Table 220 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- Immunogenicity sub-cohort 2)

All subjects except immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 27.4% subjects in the HRV group and 29.6% subjects in the placebo group Table 218).
- Irritability/fussiness was reported for 21.5% [95% CI: 19.4%; 23.6%] and 12.9% [95% CI: 11.2%; 14.7%] subjects after the first and second dose of HRV vaccine, respectively (Table 217).

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 36.6% subjects in the HRV group and 34.0% subjects in the placebo group. No more than 3.3% of the subjects in both groups reported irritability/fussiness rated as grade “3” in intensity (Table 220).
- Irritability/fussiness was reported for 28.8% [95% CI: 21.7%; 36.6%] and 18.7% [95% CI: 12.8%; 25.8%] subjects after the first and second dose of HRV vaccine, respectively (Table 219). Fever was reported for 3.9% subjects in the HRV group and 4.6% subjects in the placebo group (Table 220).

### 8.2.4. Unsolicited adverse events

The results are detailed in the following tables:

Table 221 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

Table 222 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

Table 223 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 18.6% in the HRV group and 22.1% in the placebo group (Table 221).
- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one grade “3” unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 0.1% in the HRV group and 0.2% in the placebo group (Table 223).
- The percentage of subjects reported for unsolicited AEs assessed as causally related to vaccination was 0.5% in the HRV group and 0.4% in the placebo group (Table 225).

## 8.3. According-to-protocol cohort analysis

The analysis of safety was based on the TVC. As the percentage of enrolled subjects excluded from the ATP cohort for safety was lower than 5% in both groups, no analysis based on the ATP cohort was performed.

## 8.4. Serious adverse events

During the study period, the percentage of subjects reported for at least one SAE was 11.0% (183/1666) in the HRV group and 14.8% (246/1667) in the placebo group. [redacted] None of the SAEs reported in the HRV group were causally related to the vaccine as assessed by the investigator. [redacted] The serious adverse event (SAE) Summary Table(s) are in Section 14.1 and the SAE CIOMS reports are in Section 14.2.

### 8.4.1. Fatal events

Of the 13 deaths (6 in the HRV group and 7 in the placebo group) reported during the study period, none were assessed as causally related to vaccination by the investigator (Table 240 and section 14.1).

### 8.4.2. Non-fatal events

A total of 659 SAEs (289 in the HRV group and 370 in the placebo group) were reported throughout the study (Section 14.1).

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

Eighteen subjects (8 in the HRV group and 10 in the placebo group) experienced unsolicited AEs or SAEs, leading to premature discontinuation from the study (Table 241).

Placebo group

- [redacted] This subject experienced the SAE four days post-Dose 1 of the placebo and it lasted for a period of 8 days. The subject was hospitalised and the outcome of the SAE was recovered/resolved. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the AE 22 days post-Dose 1 of the placebo and the end date was reported as “missing confirmed”. The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.

- [redacted] This subject experienced the AE 14 days post-Dose 1 of the placebo and the end date was reported as "missing confirmed". The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.
- [redacted] This subject experienced the SAE 356 days post-Dose 2 of the placebo, it lasted for a period of 30 days and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the AE three days post-Dose 1 of the placebo it lasted for a period of 39 days. The subject was treated and the outcome was recovered/resolved. The AE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE one day post-Dose 1 of the placebo it lasted for a period of 21 days. The subject was hospitalized and the outcome was recovered/resolved. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE 18 days post-Dose 2 of the placebo, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE 530 days post-Dose 2 of the placebo, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE 36 days post-Dose 2 of the placebo, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAEs 107 days and 111 days post-Dose 2 of the placebo, respectively. The SAEs lasted for period of 5 days and one day, respectively, and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.

HRV group

- [redacted] This subject experienced the SAE 496 days post-Dose 2 of the HRV vaccine and it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the AE nine days post-Dose 1 of the HRV vaccine and the end date was

reported as "missing confirmed". The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.

- [redacted] This subject experienced the AE seven days post-Dose 1 of the HRV vaccine and the end date was reported as "missing confirmed". The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.
- [redacted] The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 2 days post-Dose 1 of the HRV vaccine and it lasted for two days and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 118 days post-Dose 2 of the HRV vaccine, it lasted for a period of 47 days and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 95 days post-Dose 2 of the HRV vaccine, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 218 days post-Dose 2 of the HRV vaccine, it lasted for four days and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.

## 8.6. Concomitant medications /vaccinations

The results are detailed in the following tables:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects who received any concomitant medication was 9.5% in the HRV group and 11.5% in the placebo group. Antipyretic and antibiotic medications were received by 1.2% and 2.7% subjects in the HRV group and 2% and 3.8% subjects in the placebo group, respectively (Table 244).
- During the study period, the percentage of subjects who received any concomitant medication was 34.6% in the HRV group and 38.6% in the placebo group. Antipyretic and antibiotic medications were received by 7.3% and 18.6% subjects in the HRV group and 8.6% and 22.5% subjects in the placebo group, respectively (Table 245).

## 8.7. Safety summary

*Any Symptom:*

All subjects except immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any AEs (solicited or unsolicited) was 44.2% [95% CI: 41.7%; 46.8%] subjects in the HRV group and 47.3% [95% CI: 44.8%; 49.8%] subjects in the placebo group. Any AEs (solicited or unsolicited) were reported for 32.8% [95% CI: 30.4%; 35.2%] and 26.6% [95% CI: 24.4%; 29.0%] subjects after the first and second dose of HRV vaccine respectively. Any AEs (solicited or unsolicited) assessed as causally related to vaccination were reported by 15.8% [95% CI: 14.0%; 17.7%] subjects in HRV group and 14.7% [95% CI: 12.9%; 16.5%] subjects in the placebo group. No more than 11.2% of the subjects in both groups reported any AEs (solicited or unsolicited) rated as grade “3” in intensity.

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any general symptoms (solicited or unsolicited) was 52.9% [95% CI 44.7%; 61.1%] subjects in the HRV group and 50.3% [95% CI: 42.1%; 58.5%] subjects in the placebo group. Any general symptoms (solicited or unsolicited) were reported for 42.5% [95% CI: 34.5%; 50.7%] and 30.0% [95% CI: 22.8%; 38.0%] subjects after the first and second dose of HRV vaccine, respectively. No more than 16.0% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade “3” in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.
- During the 8-day follow-up period (Day 0 to Day 7), any general symptoms (solicited or unsolicited) rated as grade “3” in intensity and causally related to vaccination were reported for 2.6% [95% CI: 0.7%; 6.6%] subjects in the HRV group and 2.0% [95% CI: 0.4%; 5.6%] subjects in the placebo group. No more than 1.3% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade “3” in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.

- During the 8-day follow-up period (Day 0 to Day 7), any AEs (solicited or unsolicited) requiring medical attention were reported for 12.4% [95% CI: 7.6%; 18.7%] subjects in the HRV group and 11.1% [95% CI: 6.6%; 17.2%] subjects in the placebo group.

*Solicited symptoms:*

All subjects except immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 27.4% subjects in the HRV group and 29.6% subjects in the placebo group. Irritability/fussiness was reported for 21.5% [95% CI: 19.4%; 23.6%] and 12.9% [95% CI: 11.2%; 14.7%] subjects after the first and second dose of HRV vaccine, respectively.

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 36.6% subjects in the HRV group and 34.0% subjects in the placebo group. Irritability/fussiness was reported for 28.8% [95% CI: 21.7%; 36.6%] and 18.7% [95% CI: 12.8%; 25.8%] subjects after the first and second dose of HRV vaccine, respectively. No more than 3.3% of the subjects in both groups reported irritability/fussiness rated as grade "3" in intensity.
- During the 8-day (Day 0- Day 7) follow-up period, redness was the most frequently reported solicited local symptom for 13.3% subjects in the HRV group and 8.6% subjects in the placebo group. The most frequently reported grade "3" solicited local AEs were pain for 1.3% of subjects in the HRV group and redness for 0.7% of subjects in the placebo group. The solicited local symptoms were related to DTPa vaccine given intramuscularly.

All subjects:

*Unsolicited symptoms:*

- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 18.6% in the HRV group and 22.1% in the placebo group.
- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one grade "3" unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 0.1% in the HRV group and 0.2% in the placebo group. The percentage of subjects reported for unsolicited AEs assessed as causally related to vaccination was 0.5% in the HRV group and 0.4% in the placebo group.

*Serious adverse events:*

- During the study period, the percentage of subjects reported for at least one SAE was 11.0% (183/1666) in the HRV group and 14.8% (246/1667) in the placebo group. [redacted] None of the SAEs reported in the HRV group were causally related to the vaccine as assessed by the investigator. [redacted]
- Of the 13 deaths (6 in the HRV group and 7 in the placebo group) reported during the study period, none of the fatal SAEs were assessed as causally related to vaccination by the investigator.

*Withdrawals due to adverse events /serious adverse events:*

- Eighteen subjects (8 in the HRV group and 10 in the placebo group) experienced unsolicited AEs or SAEs, leading to premature discontinuation from the study.

# 9. DISCUSSION

This phase III, double-blind study was conducted to evaluate the efficacy of two doses of the liquid HRV vaccine in the Chinese population from 2 weeks post-dose 2 up to approximately two years of age. The safety of the liquid HRV vaccine was also evaluated.

Two doses of the HRV vaccine were found to be efficacious against severe RV GE from 2 weeks after Dose 2 up to Visit 7 [72.0% (95% CI: 54.1%; 83.6%; p-value: <0.001)]. VE against severe RV GE from 2 weeks after Dose 2 up to Visit 6 was 75.0% [95% CI: 44.7%; 90.1%] and from after visit 6 up to Visit 7 was 70.2% [95% CI: 43.5%; 85.3%]. The observed vaccine efficacy against severe RV GE in this study is in the range of the results of studies conducted in Latin America (84.7%) [95% CI: 71.1%; 92.4%] [Ruiz Palacios, 2006] and Africa (61.2%) [95% CI: 44.0%; 73.2%] [Madhi, 2010] but lower than what was observed in developed Asian countries (96.1%) [95% CI: 85.1%; 99.5%] [Phua, 2012] and EU (96%) [95% CI: 90.0%; 99.0%] [Vesikari, 2007]. Potential factors that may have contributed to the difference in estimates might include seasonality, time of enrolment in relation with the rotavirus season, the level of rotavirus exposure in the placebo group, differences in severity of RV GE episodes and potential differences in underlying host characteristics.

In this study, G1P[8] and G2P[4] were the most prevalent G1 and non-G1 RV strains identified from GE stool samples collected. Vaccine efficacy observed against any and severe RV GE caused by circulating wild type G1 RV from 2 weeks after Dose 2 up to Visit 7 was 52.2% [95% CI: 19.0%; 72.6%] and 64.0% [95% CI: 20.4%; 85.2%], respectively. Vaccine efficacy observed against any and severe GE caused by non-G1 RV from 2 weeks after Dose 2 up to Visit 7 was 62.1% [95% CI: 46.9%; 73.3%] and 77.8% [95% CI: 58.0%; 89.2%], respectively. A protection against RV GE caused by G2P[4] was demonstrated in this study.

The exploratory analysis performed using the Cox model showed that a total of 2.7 episodes of severe RV GE could be prevented per 100 infants vaccinated per year.

There were very few cases of hospitalised RV GE in the HRV vaccine group as compared to the placebo group (four subjects versus twenty one subjects) during the study period. Vaccine efficacy against hospitalisations due to severe RV GE was 81.0% [95% CI: 43.6%; 95.3%] and is comparable to the other efficacy trials conducted in the past: 92.4% [95% CI: 82.2; 98.8] [Phua, 2012] and 71.5% [95% CI: 53.4%; 82.9%] [Vesikari, 2007]. The burden associated with hospitalized RV GE in China is substantial as RV GE accounted for 32% - 50% of the hospitalised diarrhoea [Naghipour, 2008; Wang, 2009], and it could be reduced through the introduction of RV vaccines.

The safety profile was similar in both groups. The percentage of subjects with SAEs and AEs/SAEs leading to drop out was comparable in both groups. Two cases of intussusception (one in HRV group and one in placebo group) were reported during the study period and none of the cases were assessed as causally related to vaccination. From Dose 1 up to Visit 7, there were a total of 13 fatal events (6 subjects in the HRV group and 7 subjects in the placebo group). Overall, the vaccine efficacy results obtained after 2

doses of liquid HRV vaccine are promising and indicate that including this vaccine in the public health programmes in countries with high incidence of RV GE would be of significant public health value.

# 10. OVERALL CONCLUSIONS (SUMMARY)

- Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV during the efficacy follow up period (2 weeks post-Dose 2 up to Visit 7) was 72.0% (95% CI: 54.1%; 83.6%). The primary objective of this study was met.

# 11. TABLES AND FIGURES

## 11.1. Subject eligibility and attrition from the study

### 11.1.1. Number of subjects

**Table 14 Number of subjects by centre (Total vaccinated cohort)**

| | HRV | Placebo | Total | |
|---|---|---|---|---|
| Center | n | n | n | % |
| [redacted] | 600 | 600 | 1200 | 36.0 |
| [redacted] | 452 | 452 | 904 | 27.1 |
| [redacted] | 461 | 462 | 923 | 27.7 |
| [redacted] | 153 | 153 | 306 | 9.2 |
| All | 1666 | 1667 | 3333 | 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

**Table 15 Subjects unblinded before database lock (13AUG2012) (Total vaccinated cohort)**

[redacted]

Day of onset: relative to previous dose administered (administration day is day 0)

**Table 16 Number of subjects in the sub-cohorts (Total vaccinated cohort)**

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| Characteristics | Categories | n | % | n | % | n | % |
| Sub-cohort | Immunogenicity sub cohort 1 | 306 | 18.4 | 306 | 18.4 | 612 | 18.4 |
| | Immunogenicity sub cohort 2 | 153 | 9.2 | 153 | 9.2 | 306 | 9.2 |
| | All subjects except immunogenicity sub cohorts | 1207 | 72.4 | 1208 | 72.5 | 2415 | 72.5 |

N = number of subject number
n = number of subject number in a given category
% = n / Number of subject number with available results x 100
All subjects except immunogenicity sub cohorts - contains all the subjects for whom there is no blood sample planned in the study.

## 11.1.2. Study completion and withdrawal from study

### Table 17 Number of subjects entered, completed and withdrawn with reason for withdrawal till Visit 7 (Total vaccinated cohort)

| | HRV | Placebo | Total |
|---|---|---|---|
| **Number of subjects vaccinated** | 1666 | 1667 | 3333 |
| **Number of subjects completed** | 1518 | 1499 | 3017 |
| **Number of subjects withdrawn** | 148 | 168 | 316 |
| **Reasons for withdrawal :** | | | |
| Serious Adverse Event | 6 | 7 | 13 |
| Non-Serious Adverse Event | 4 | 8 | 12 |
| Protocol violation | 0 | 0 | 0 |
| Consent withdrawal (not due to an adverse event) | 55 | 46 | 101 |
| Migrated/moved from study area | 23 | 24 | 47 |
| Lost to follow-up (subjects with incomplete vaccination course) | 0 | 0 | 0 |
| Lost to follow-up (subjects with complete vaccination course) | 0 | 0 | 0 |
| Sponsor study termination | 0 | 0 | 0 |
| Other - diarrhea | 1 | 0 | 1 |
| Other - not willing to participate in the extended follow-up* (visit 7) | 59 | 83 | 142 |

Vaccinated= number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
*Second year follow up

### Table 18 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

| | Total | | | HRV | | Placebo | | NOGRP | |
|---|---|---|---|---|---|---|---|---|---|
| Title | n | s | % | n | s | n | s | n | s |
| Total cohort | 3340 | | | 1667 | | 1667 | | 6 | |
| Study vaccine dose not administrated but subject number allocated ( code 1030 ) | 7 | 7 | | 1 | 1 | 0 | 0 | 6 | 6 |
| Total vaccinated cohort | 3333 | | 100 | 1666 | | 1667 | | 0 | |
| Administration of vaccine(s) forbidden in the protocol ( code 1040 ) | 2 | 2 | | 1 | 1 | 1 | 1 | 0 | 0 |
| Randomisation code broken at the investigator site ( code 1060 ) | 2 | 2 | | 0 | 0 | 2 | 2 | 0 | 0 |
| Study vaccine dose not administered according to protocol ( code 1070 ) | 41 | 41 | | 22 | 22 | 19 | 19 | 0 | 0 |
| ATP cohort for safety | 3288 | | 98.6 | 1643 | | 1645 | | 0 | |
| At least one study vaccine dose not administered ( code 3010 ) | 133 | 137 | | 66 | 67 | 67 | 70 | 0 | 0 |
| Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response ( code 3030 ) | 7 | 8 | | 2 | 2 | 5 | 6 | 0 | 0 |
| ATP cohort for efficacy | 3148 | | 94.4 | 1575 | | 1573 | | 0 | |
| Subjects who do not have follow-up beyond visit 6 ( code 4020 ) | 169 | 307 | | 75 | 143 | 94 | 164 | 0 | 0 |
| ATP cohort for efficacy for second year follow-up | 2979 | | 89.4 | 1500 | | 1479 | | 0 | |

NOGRP = No assigned group
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

## 11.1.3. Protocol deviations

### Table 19 Protocol deviations not leading to exclusion of subjects or their data from analysis

| Protocol Deviation | Number of Subjects (%) |
|---|---|
| Non compliance to visit schedule | 71 |
| Vaccine administration in spite of storage temperature deviation outside recommended range | 34 |
| Inclusion/Exclusion criteria deviation | 31 |
| Administration of forbidden medication/Vaccine | 7 |
| Post-vaccination observation time less than 30 min | 7 |
| Stool sample shipment delayed by more than 3 days | 4 |
| Non-compliance to blood sampling schedule withdrawn refused for subject | 3 |
| Non investigational rotavirus vaccine administration | 2 |
| Blood withdrawn from subject belonging to non-immuno cohort | 2 |
| Delay in informing parents about the Subject Information Letter (Version 1 dated 13 October 2010) | 2 |
| Concomitant vaccination outside study centre | 2 |
| Delayed reporting of SAE | 1 |
| Body temperature not taken before vaccination | 1 |
| Concomitant vaccination outside visit window | 1 |
| Total | 168 |

# 11.2. Demographic characteristics

## 11.2.1. ATP cohort for efficacy

### Table 20 Summary of demographic characteristics (ATP cohort for efficacy)

| | | HRV N = 1575 | | Placebo N = 1573 | | Total N = 3148 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.5 | - | 9.7 | - | 9.6 | - |
| | SD | 2.63 | - | 2.56 | - | 2.60 | - |
| | Median | 9.0 | - | 9.0 | - | 9.0 | - |
| | Minimum | 5 | - | 5 | - | 5 | - |
| | Maximum | 16 | - | 16 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.1 | - | 14.2 | - | 14.1 | - |
| | SD | 2.78 | - | 2.64 | - | 2.71 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 9 | - | 10 | - | 9 | - |
| | Maximum | 26 | - | 22 | - | 26 | - |
| Age (months) at visit 6/last contact | Mean | 11.4 | - | 11.4 | - | 11.4 | - |
| | SD | 0.64 | - | 0.68 | - | 0.66 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 4 | - | 3 | - | 3 | - |
| | Maximum | 15 | - | 18 | - | 18 | - |
| Age (months) at visit 7 | Mean | 19.7 | - | 19.8 | - | 19.8 | - |
| | SD | 1.42 | - | 1.37 | - | 1.40 | - |
| | Median | 20.0 | - | 20.0 | - | 20.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 80 | - | 98 | - | 178 | - |
| Gender | Female | 758 | 48.1 | 793 | 50.4 | 1551 | 49.3 |
| | Male | 817 | 51.9 | 780 | 49.6 | 1597 | 50.7 |
| Geographic Ancestry | Asian-Chinese heritage | 1575 | 100 | 1573 | 100 | 3148 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 21 Summary of vital signs characteristics at Visit 1 (Day 0) (ATP cohort for efficacy)

| | | HRV (N = 1575) | Placebo (N = 1573) | Total (N = 3148) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.8 | 59.0 | 58.9 |
| | SD | 2.92 | 2.91 | 2.92 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 49.0 | 46.0 | 46.0 |
| | Maximum | 70.0 | 72.0 | 72.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.6 | 5.7 | 5.7 |
| | SD | 0.84 | 0.85 | 0.84 |
| | Median | 5.6 | 5.7 | 5.6 |
| | Minimum | 3.0 | 3.0 | 3.0 |
| | Maximum | 9.5 | 9.0 | 9.5 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 16.3 | 16.3 | 16.3 |
| | SD | 1.84 | 1.88 | 1.86 |
| | Median | 16.1 | 16.3 | 16.1 |
| | Minimum | 11.7 | 8.9 | 8.9 |
| | Maximum | 25.5 | 26.8 | 26.8 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.26 | 1.25 | 1.25 |
| | Median | 39.3 | 39.4 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## 11.2.2. Total Vaccinated cohort

### Table 22 Summary of demographic characteristics (Total Vaccinated cohort)

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.5 | - | 9.7 | - | 9.6 | - |
| | SD | 2.64 | - | 2.59 | - | 2.62 | - |
| | Median | 9.0 | - | 9.0 | - | 9.0 | - |
| | Minimum | 5 | - | 5 | - | 5 | - |
| | Maximum | 16 | - | 16 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.1 | - | 14.2 | - | 14.1 | - |
| | SD | 2.79 | - | 2.64 | - | 2.72 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 9 | - | 10 | - | 9 | - |
| | Maximum | 26 | - | 22 | - | 26 | - |
| | Unknown | 67 | - | 70 | - | 137 | - |
| Age (months) at visit 6/last contact | Mean | 11.1 | - | 11.1 | - | 11.1 | - |
| | SD | 1.68 | - | 1.69 | - | 1.69 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 2 | - | 2 | - | 2 | - |
| | Maximum | 15 | - | 18 | - | 18 | - |
| Age (months) at visit 7 | Mean | 19.7 | - | 19.8 | - | 19.8 | - |
| | SD | 1.43 | - | 1.38 | - | 1.40 | - |
| | Median | 20.0 | - | 20.0 | - | 20.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 148 | - | 168 | - | 316 | - |
| Gender | Female | 795 | 47.7 | 836 | 50.1 | 1631 | 48.9 |
| | Male | 871 | 52.3 | 831 | 49.9 | 1702 | 51.1 |
| Geographic Ancestry | Asian-Chinese heritage | 1666 | 100 | 1667 | 100 | 3333 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 23 Summary of demographic characteristics (Total vaccinated cohort-Immunogenicity sub cohort 1)

| | | HRV N = 306 | | Placebo N = 306 | | Total N = 612 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 10.2 | - | 10.1 | - | 10.2 | - |
| | SD | 2.97 | - | 2.81 | - | 2.89 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 5 | - | 6 | - | 5 | - |
| | Maximum | 16 | - | 15 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.7 | - | 14.6 | - | 14.6 | - |
| | SD | 3.10 | - | 2.93 | - | 3.01 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 10 | - | 10 | - | 10 | - |
| | Maximum | 23 | - | 22 | - | 23 | - |
| | Unknown | 18 | - | 19 | - | 37 | - |
| Age (months) at visit 6/last contact | Mean | 10.9 | - | 10.9 | - | 10.9 | - |
| | SD | 1.97 | - | 1.99 | - | 1.98 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 2 | - | 2 | - | 2 | - |
| | Maximum | 14 | - | 13 | - | 14 | - |
| Age (months) at visit 7 | Mean | 21.0 | - | 20.9 | - | 21.0 | - |
| | SD | 1.00 | - | 0.93 | - | 0.97 | - |
| | Median | 21.0 | - | 21.0 | - | 21.0 | - |
| | Minimum | 19 | - | 19 | - | 19 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 34 | - | 39 | - | 73 | - |
| Gender | Female | 153 | 50.0 | 153 | 50.0 | 306 | 50.0 |
| | Male | 153 | 50.0 | 153 | 50.0 | 306 | 50.0 |
| Geographic Ancestry | Asian-Chinese heritage | 306 | 100 | 306 | 100 | 612 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 24 Summary of demographic characteristics (Total vaccinated cohort-Immunogenicity sub cohort 2)

| | | HRV N = 153 | | Placebo N = 153 | | Total N = 306 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.8 | - | 10.1 | - | 10.0 | - |
| | SD | 1.30 | - | 1.29 | - | 1.30 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 8 | - | 8 | - | 8 | - |
| | Maximum | 12 | - | 12 | - | 12 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.3 | - | 14.6 | - | 14.5 | - |
| | SD | 1.27 | - | 1.32 | - | 1.30 | - |
| | Median | 14.0 | - | 15.0 | - | 14.0 | - |
| | Minimum | 12 | - | 12 | - | 12 | - |
| | Maximum | 17 | - | 17 | - | 17 | - |
| | Unknown | 3 | - | 2 | - | 5 | - |
| Age (months) at visit 6/last contact | Mean | 11.2 | - | 11.2 | - | 11.2 | - |
| | SD | 1.19 | - | 1.30 | - | 1.24 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 5 | - | 3 | - | 3 | - |
| | Maximum | 14 | - | 13 | - | 14 | - |
| Age (months) at visit 7 | Mean | 18.9 | - | 19.0 | - | 19.0 | - |
| | SD | 1.12 | - | 1.14 | - | 1.13 | - |
| | Median | 19.0 | - | 19.0 | - | 19.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 21 | - | 21 | - | 21 | - |
| | Unknown | 15 | - | 12 | - | 27 | - |
| Gender | Female | 72 | 47.1 | 82 | 53.6 | 154 | 50.3 |
| | Male | 81 | 52.9 | 71 | 46.4 | 152 | 49.7 |
| Geographic Ancestry | Asian-Chinese heritage | 153 | 100 | 153 | 100 | 306 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 25 Summary of demographic characteristics (Total vaccinated cohort-except Immunogenicity sub cohorts)

| | | HRV N = 1207 | | Placebo N = 1208 | | Total N = 2415 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.3 | - | 9.6 | - | 9.4 | - |
| | SD | 2.65 | - | 2.64 | - | 2.65 | - |
| | Median | 9.0 | - | 9.0 | - | 9.0 | - |
| | Minimum | 6 | - | 5 | - | 5 | - |
| | Maximum | 16 | - | 16 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 13.9 | - | 14.0 | - | 14.0 | - |
| | SD | 2.83 | - | 2.68 | - | 2.76 | - |
| | Median | 13.0 | - | 14.0 | - | 13.0 | - |
| | Minimum | 9 | - | 10 | - | 9 | - |
| | Maximum | 26 | - | 21 | - | 26 | - |
| | Unknown | 46 | - | 49 | - | 95 | - |
| Age (months) at visit 6/last contact | Mean | 11.2 | - | 11.1 | - | 11.2 | - |
| | SD | 1.65 | - | 1.65 | - | 1.65 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 2 | - | 2 | - | 2 | - |
| | Maximum | 15 | - | 18 | - | 18 | - |
| Age (months) at visit 7 | Mean | 19.5 | - | 19.6 | - | 19.6 | - |
| | SD | 1.38 | - | 1.33 | - | 1.36 | - |
| | Median | 19.0 | - | 19.0 | - | 19.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 99 | - | 117 | - | 216 | - |
| Gender | Female | 570 | 47.2 | 601 | 49.8 | 1171 | 48.5 |
| | Male | 637 | 52.8 | 607 | 50.2 | 1244 | 51.5 |
| Geographic Ancestry | Asian-Chinese heritage | 1207 | 100 | 1208 | 100 | 2415 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 26 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort)

| | | HRV (N = 1666) | Placebo (N = 1667) | Total (N = 3333) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.8 | 59.0 | 58.9 |
| | SD | 2.93 | 2.93 | 2.93 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 49.0 | 46.0 | 46.0 |
| | Maximum | 70.0 | 72.0 | 72.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.7 | 5.7 | 5.7 |
| | SD | 0.85 | 0.85 | 0.85 |
| | Median | 5.6 | 5.7 | 5.6 |
| | Minimum | 3.0 | 3.0 | 3.0 |
| | Maximum | 9.5 | 9.0 | 9.5 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 16.3 | 16.4 | 16.3 |
| | SD | 1.84 | 1.87 | 1.85 |
| | Median | 16.1 | 16.3 | 16.2 |
| | Minimum | 11.7 | 8.9 | 8.9 |
| | Maximum | 25.5 | 26.8 | 26.8 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.25 | 1.26 | 1.25 |
| | Median | 39.3 | 39.3 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## Table 27 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort- Immunogenicity sub cohort 1)

| | | HRV (N = 306) | Placebo (N = 306) | Total (N = 612) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 59.2 | 59.3 | 59.3 |
| | SD | 2.84 | 2.91 | 2.87 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 52.0 | 46.0 | 46.0 |
| | Maximum | 68.0 | 67.0 | 68.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.6 | 5.6 | 5.6 |
| | SD | 0.85 | 0.83 | 0.84 |
| | Median | 5.4 | 5.7 | 5.5 |
| | Minimum | 3.7 | 3.4 | 3.4 |
| | Maximum | 8.3 | 7.9 | 8.3 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 15.8 | 16.0 | 15.9 |
| | SD | 1.59 | 1.74 | 1.67 |
| | Median | 15.6 | 15.9 | 15.8 |
| | Minimum | 11.7 | 11.1 | 11.1 |
| | Maximum | 20.8 | 22.2 | 22.2 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.36 | 1.29 | 1.33 |
| | Median | 39.3 | 39.3 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## Table 28 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort- Immunogenicity sub cohort 2)

| | | HRV (N = 153) | Placebo (N = 153) | Total (N = 306) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.8 | 59.4 | 59.1 |
| | SD | 2.86 | 2.62 | 2.76 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 50.0 | 53.0 | 50.0 |
| | Maximum | 67.0 | 67.0 | 67.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 6.0 | 6.0 | 6.0 |
| | SD | 0.83 | 0.78 | 0.81 |
| | Median | 6.0 | 6.0 | 6.0 |
| | Minimum | 3.0 | 3.8 | 3.0 |
| | Maximum | 9.5 | 8.0 | 9.5 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 17.4 | 17.0 | 17.2 |
| | SD | 1.90 | 1.93 | 1.92 |
| | Median | 17.2 | 16.9 | 16.9 |
| | Minimum | 12.0 | 11.3 | 11.3 |
| | Maximum | 25.5 | 23.9 | 25.5 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.5 | 39.4 |
| | SD | 1.11 | 1.22 | 1.17 |
| | Median | 39.3 | 39.4 | 39.4 |
| | Minimum | 36.6 | 36.3 | 36.3 |
| | Maximum | 42.0 | 42.4 | 42.4 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## Table 29 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort- except immunogenicity sub cohorts)

| | | HRV (N = 1207) | Placebo (N = 1208) | Total (N = 2415) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.7 | 58.9 | 58.8 |
| | SD | 2.95 | 2.96 | 2.95 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 49.0 | 51.0 | 49.0 |
| | Maximum | 70.0 | 72.0 | 72.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.6 | 5.7 | 5.7 |
| | SD | 0.84 | 0.86 | 0.85 |
| | Median | 5.6 | 5.6 | 5.6 |
| | Minimum | 3.1 | 3.0 | 3.0 |
| | Maximum | 9.4 | 9.0 | 9.4 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 16.3 | 16.4 | 16.3 |
| | SD | 1.83 | 1.88 | 1.85 |
| | Median | 16.1 | 16.4 | 16.3 |
| | Minimum | 11.9 | 8.9 | 8.9 |
| | Maximum | 24.6 | 26.8 | 26.8 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.24 | 1.25 | 1.25 |
| | Median | 39.3 | 39.3 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## 11.3. Concomitant and Intercurrent Vaccinations

### Table 30 Summary of co-administered vaccination by dose (Total vaccinated cohort- except immunogenicity sub cohort 2)

| | HRV N = 1513 | | Placebo N = 1514 | | Total N = 3027 | |
|---|---|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Dose 1** | | | | | | |
| Any | 4 | 0.3 | 5 | 0.3 | 9 | 0.3 |
| DPT | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| HBV | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| OPV | 2 | 0.1 | 5 | 0.3 | 7 | 0.2 |
| **Dose 2** | | | | | | |
| | **HRV N = 1449** | | **Placebo N = 1446** | | **Total N = 2895** | |
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any | 4 | 0.3 | 5 | 0.3 | 9 | 0.3 |
| DPT | 2 | 0.1 | 3 | 0.2 | 5 | 0.2 |
| HBV | 0 | 0.0 | 1 | 0.1 | 1 | 0.0 |
| OPV | 3 | 0.2 | 4 | 0.3 | 7 | 0.2 |

N= total number of subjects having received the considered dose of HRV/placebo
n/%= number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

**Table 31 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort- except immunogenicity sub cohort 2)**

| Before Dose 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV N = 1513 | | | Placebo N = 1514 | | | Total N = 3027 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 5179 | 1510 | 99.8 | 5220 | 1514 | 100 | 10399 | 3024 | 99.9 |
| BCG | 1508 | 1508 | 99.7 | 1510 | 1510 | 99.7 | 3018 | 3018 | 99.7 |
| DPT | 89 | 89 | 5.9 | 79 | 79 | 5.2 | 168 | 168 | 5.6 |
| DTPa | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 2944 | 1509 | 99.7 | 2964 | 1514 | 100 | 5908 | 3023 | 99.9 |
| HIB | 1 | 1 | 0.1 | 1 | 1 | 0.1 | 2 | 2 | 0.1 |
| OPV | 637 | 552 | 36.5 | 665 | 588 | 38.8 | 1302 | 1140 | 37.7 |
| **Between dose 1 and dose 2$** | | | | | | | | | |
| | HRV N = 1513 | | | Placebo N = 1514 | | | Total N = 3027 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 1713 | 1198 | 79.2 | 1776 | 1221 | 80.6 | 3489 | 2419 | 79.9 |
| BCG | 3 | 3 | 0.2 | 2 | 2 | 0.1 | 5 | 5 | 0.2 |
| DPT | 458 | 447 | 29.5 | 499 | 491 | 32.4 | 957 | 938 | 31.0 |
| HBV | 56 | 56 | 3.7 | 52 | 52 | 3.4 | 108 | 108 | 3.6 |
| HIB | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| OPV | 1195 | 1170 | 77.3 | 1223 | 1197 | 79.1 | 2418 | 2367 | 78.2 |
| **Between dose 2 and visit 3*** | | | | | | | | | |
| | HRV N = 1449 | | | Placebo N = 1446 | | | Total N = 2895 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 2670 | 1339 | 92.4 | 2676 | 1329 | 91.9 | 5346 | 2668 | 92.2 |
| DPT | 1304 | 1260 | 87.0 | 1333 | 1292 | 89.3 | 2637 | 2552 | 88.2 |
| FLU | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 20 | 20 | 1.4 | 9 | 9 | 0.6 | 29 | 29 | 1.0 |
| HIB | 0 | 0 | 0.0 | 4 | 3 | 0.2 | 4 | 3 | 0.1 |
| JE | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| MMR | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| MPSV | 6 | 5 | 0.3 | 2 | 2 | 0.1 | 8 | 7 | 0.2 |
| MR | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| OPV | 1337 | 1281 | 88.4 | 1323 | 1273 | 88.0 | 2660 | 2554 | 88.2 |

N= Before Dose 1 and between Dose 1 and Dose 2: total number of subjects having received dose 1 of HRV
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV 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 doses
$= upto last contact conclusion at Visit 3 if dose 2 of HRV was not administered
*= upto last contact conclusion at Visit 3 if visit 3 was not done

## Table 32 Summary of co-administered vaccination by dose (Total vaccinated cohort- Immunogenicity sub cohort 2)

| Dose 1 | | | | | | |
|---|---|---|---|---|---|---|
| | HRV N = 153 | | Placebo N = 153 | | Total N = 306 | |
| Characteristics | n | % | n | % | n | % |
| Any | 2 | 1.3 | 3 | 2.0 | 5 | 1.6 |
| BCG | 1 | 0.7 | 0 | 0.0 | 1 | 0.3 |
| HBV | 1 | 0.7 | 3 | 2.0 | 4 | 1.3 |
| **Dose 2** | | | | | | |
| | HRV N = 150 | | Placebo N = 151 | | Total N = 301 | |
| Characteristics | n | % | n | % | n | % |
| Any | 1 | 0.7 | 0 | 0.0 | 1 | 0.3 |
| HBV | 1 | 0.7 | 0 | 0.0 | 1 | 0.3 |

N= total number of subjects having received the considered dose of HRV/placebo
n/%= number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

## Table 33 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort- Immunogenicity sub cohort 2)

| Before Dose 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV N = 153 | | | Placebo N = 153 | | | Total N = 306 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 449 | 153 | 100 | 447 | 152 | 99.3 | 896 | 305 | 99.7 |
| BCG | 150 | 150 | 98.0 | 152 | 152 | 99.3 | 302 | 302 | 98.7 |
| HBV | 299 | 153 | 100 | 295 | 152 | 99.3 | 594 | 305 | 99.7 |
| **Between dose 1 and dose 2$** | | | | | | | | | |
| | HRV N = 153 | | | Placebo N = 153 | | | Total N = 306 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 4 | 3 | 2.0 | 8 | 7 | 4.6 | 12 | 10 | 3.3 |
| BCG | 1 | 1 | 0.7 | 1 | 1 | 0.7 | 2 | 2 | 0.7 |
| DPT | 0 | 0 | 0.0 | 1 | 1 | 0.7 | 1 | 1 | 0.3 |
| HBV | 3 | 3 | 2.0 | 6 | 6 | 3.9 | 9 | 9 | 2.9 |
| **Between dose 2 and visit 3*** | | | | | | | | | |
| | HRV N = 150 | | | Placebo N = 151 | | | Total N = 301 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 1 | 1 | 0.7 | 1 | 1 | 0.7 | 2 | 2 | 0.7 |
| HBV | 1 | 1 | 0.7 | 1 | 1 | 0.7 | 2 | 2 | 0.7 |

N= Before Dose 1 and between Dose 1 and Dose 2: total number of subjects having received dose 1 of HRV
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV 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 doses
% = n / Number of subject number with available results x 100
$= upto last contact conclusion at Visit 3 if dose 2 of HRV was not administered
*= upto last contact conclusion at Visit 3 if visit 3 was not done

## Table 34 Summary of co-administered vaccination by dose (Total vaccinated cohort)

| Dose 1 | | | | | | |
|---|---|---|---|---|---|---|
| | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any | 6 | 0.4 | 8 | 0.5 | 14 | 0.4 |
| BCG | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| DPT | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| HBV | 3 | 0.2 | 3 | 0.2 | 6 | 0.2 |
| OPV | 2 | 0.1 | 5 | 0.3 | 7 | 0.2 |
| **Dose 2** | | | | | | |
| | HRV N = 1599 | | Placebo N = 1597 | | Total N = 3196 | |
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any | 5 | 0.3 | 5 | 0.3 | 10 | 0.3 |
| DPT | 2 | 0.1 | 3 | 0.2 | 5 | 0.2 |
| HBV | 1 | 0.1 | 1 | 0.1 | 2 | 0.1 |
| OPV | 3 | 0.2 | 4 | 0.3 | 7 | 0.2 |

N= total number of subjects having received the considered dose of HRV/placebo
n/%= number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

**Table 35 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)**

| Before Dose 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV N = 1666 | | | Placebo N = 1667 | | | Total N = 3333 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 5628 | 1663 | 99.8 | 5667 | 1666 | 99.9 | 11295 | 3329 | 99.9 |
| BCG | 1658 | 1658 | 99.5 | 1662 | 1662 | 99.7 | 3320 | 3320 | 99.6 |
| DPT | 89 | 89 | 5.3 | 79 | 79 | 4.7 | 168 | 168 | 5.0 |
| DTPa | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 3243 | 1662 | 99.8 | 3259 | 1666 | 99.9 | 6502 | 3328 | 99.8 |
| HIB | 1 | 1 | 0.1 | 1 | 1 | 0.1 | 2 | 2 | 0.1 |
| OPV | 637 | 552 | 33.1 | 665 | 588 | 35.3 | 1302 | 1140 | 34.2 |
| **Between dose 1 and dose 2[$]** | | | | | | | | | |
| | HRV N = 1666 | | | Placebo N = 1667 | | | Total N = 3333 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 1717 | 1201 | 72.1 | 1784 | 1228 | 73.7 | 3501 | 2429 | 72.9 |
| BCG | 4 | 4 | 0.2 | 3 | 3 | 0.2 | 7 | 7 | 0.2 |
| DPT | 458 | 447 | 26.8 | 500 | 492 | 29.5 | 958 | 939 | 28.2 |
| HBV | 59 | 59 | 3.5 | 58 | 58 | 3.5 | 117 | 117 | 3.5 |
| HIB | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| OPV | 1195 | 1170 | 70.2 | 1223 | 1197 | 71.7 | 2418 | 2367 | 71.0 |
| **Between dose 2 and visit 3*** | | | | | | | | | |
| | HRV N = 1599 | | | Placebo N = 1597 | | | Total N = 3196 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 2671 | 1340 | 83.8 | 2677 | 1330 | 83.3 | 5348 | 2670 | 83.5 |
| DPT | 1304 | 1260 | 78.8 | 1333 | 1292 | 80.9 | 2637 | 2552 | 79.8 |
| FLU | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 21 | 21 | 1.3 | 10 | 10 | 0.6 | 31 | 31 | 1.0 |
| HIB | 0 | 0 | 0.0 | 4 | 3 | 0.2 | 4 | 3 | 0.1 |
| JE | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| MMR | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| MPSV | 6 | 5 | 0.3 | 2 | 2 | 0.1 | 8 | 7 | 0.2 |
| MR | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| OPV | 1337 | 1281 | 80.1 | 1323 | 1273 | 79.7 | 2660 | 2554 | 79.9 |

N= Before Dose 1 and between Dose 1 and Dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV/placebo
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV/placebo doses
n/%= number/percentage of subjects who received at least one specified vaccination between the considered visits excluding vaccination given on the day of HRV/placebo doses
% = n / Number of subject number with available results x 100
$= upto last contact conclusion at Visit 3 if dose 2 of HRV/placebo was not administered
*= upto last contact conclusion at Visit 3 if visit 3 was not done

## 11.4. Efficacy results

### Table 36 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | | HRV N = 1575 | | Placebo N = 1573 | | Total N = 3148 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 847 | 53.8 | 814 | 51.7 | 1661 | 52.8 |
| | 1 | 461 | 29.3 | 462 | 29.4 | 923 | 29.3 |
| | 2 | 165 | 10.5 | 197 | 12.5 | 362 | 11.5 |
| | 3 | 68 | 4.3 | 53 | 3.4 | 121 | 3.8 |
| | 4 | 17 | 1.1 | 29 | 1.8 | 46 | 1.5 |
| | 5 | 7 | 0.4 | 10 | 0.6 | 17 | 0.5 |
| | 6 | 6 | 0.4 | 4 | 0.3 | 10 | 0.3 |
| | 7 | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| | 9 | 3 | 0.2 | 1 | 0.1 | 4 | 0.1 |
| | 10 | 0 | 0.0 | 1 | 0.1 | 1 | 0.0 |
| | Any | 728 | 46.2 | 759 | 48.3 | 1487 | 47.2 |
| RVGE | 0 | 1505 | 95.6 | 1406 | 89.4 | 2911 | 92.5 |
| | 1 | 70 | 4.4 | 164 | 10.4 | 234 | 7.4 |
| | 2 | 0 | 0.0 | 3 | 0.2 | 3 | 0.1 |
| | Any | 70 | 4.4 | 167 | 10.6 | 237 | 7.5 |
| Severe GE | 0 | 1388 | 88.1 | 1367 | 86.9 | 2755 | 87.5 |
| | 1 | 172 | 10.9 | 174 | 11.1 | 346 | 11.0 |
| | 2 | 8 | 0.5 | 27 | 1.7 | 35 | 1.1 |
| | 3 | 4 | 0.3 | 5 | 0.3 | 9 | 0.3 |
| | 4 | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| | 5 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 187 | 11.9 | 206 | 13.1 | 393 | 12.5 |
| Severe RVGE | 0 | 1554 | 98.7 | 1498 | 95.2 | 3052 | 97.0 |
| | 1 | 21 | 1.3 | 75 | 4.8 | 96 | 3.0 |
| | Any | 21 | 1.3 | 75 | 4.8 | 96 | 3.0 |

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

## Table 37 Number of GE episodes reported from 2 weeks after Dose 2 up to Visit 7 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 614 | 52.6 | 654 | 52.8 |
| | Moderate (7-10) | 341 | 29.2 | 340 | 27.5 |
| | Severe (≥11) | 213 | 18.2 | 243 | 19.6 |
| | Unknown | 0 | 0.0 | 1 | 0.1 |
| | Any | 1168 | 100 | 1237 | 99.9 |
| RVGE | Mild (1-6) | 28 | 40.0 | 45 | 26.5 |
| | Moderate (7-10) | 21 | 30.0 | 50 | 29.4 |
| | Severe (≥11) | 21 | 30.0 | 75 | 44.1 |
| | Any | 70 | 100 | 170 | 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

## Table 38 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | HRV N' = 1168 | | Placebo N' = 1238 | | Total N' = 2406 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 56 | 4.8 | 67 | 5.4 | 123 | 5.1 |
| no stools collected* | 54 | 4.6 | 66 | 5.3 | 120 | 5.0 |
| stools collected but no results available | 2 | 0.2 | 1 | 0.1 | 3 | 0.1 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category
*There is one episode of GE for which sample was collected but was not sent to lab. Hence the sample was not tested.

## Table 39 Percentage of subjects with RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

| | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| Serotype | n | % | n | % |
| Any | 70 | 4.4 | 167 | 10.6 |
| G1 WT | 22 | 1.4 | 46 | 2.9 |
| G2 | 42 | 2.7 | 105 | 6.7 |
| G3 | 1 | 0.1 | 12 | 0.8 |
| G9 | 1 | 0.1 | 5 | 0.3 |
| GX | 6 | 0.4 | 8 | 0.5 |
| P4 | 43 | 2.7 | 107 | 6.8 |
| P8 WT | 25 | 1.6 | 59 | 3.8 |
| P9 | 0 | 0.0 | 1 | 0.1 |
| PX | 4 | 0.3 | 1 | 0.1 |

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=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 40 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

| | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 21 | 1.3 | 75 | 4.8 |
| G1 WT | 9 | 0.6 | 25 | 1.6 |
| G2 | 11 | 0.7 | 43 | 2.7 |
| G3 | 0 | 0.0 | 3 | 0.2 |
| G9 | 0 | 0.0 | 3 | 0.2 |
| GX | 1 | 0.1 | 6 | 0.4 |
| P4 | 12 | 0.8 | 43 | 2.7 |
| P8 WT | 9 | 0.6 | 31 | 2.0 |
| PX | 1 | 0.1 | 1 | 0.1 |

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 severe RV GE episode whatever the serotype
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 41 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=70 | | Placebo N'=170 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+G2+P4 | 0 | 0.00 | 4 | 2.35 |
| G1WT+G2+P4+P8WT | 1 | 1.43 | 1 | 0.59 |
| G1WT+G2+P8WT | 0 | 0.00 | 3 | 1.76 |
| G1WT+P4 | 1 | 1.43 | 5 | 2.94 |
| G1WT+P8WT | 19 | 27.14 | 34 | 20.00 |
| G1WT+PX | 1 | 1.43 | 0 | 0.00 |
| G2+G3+P4 | 1 | 1.43 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 0.59 |
| G2+P4 | 39 | 55.71 | 97 | 57.06 |
| G2+P4+P8WT | 1 | 1.43 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 0.59 |
| G3+P8WT | 0 | 0.00 | 10 | 5.88 |
| G3+P9 | 0 | 0.00 | 1 | 0.59 |
| G9+P8WT | 1 | 1.43 | 5 | 2.94 |
| GX | 0 | 0.00 | 2 | 1.18 |
| GX+P8WT | 3 | 4.29 | 6 | 3.53 |
| GX+PX | 3 | 4.29 | 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 2 of HRV vaccine or placebo up to visit 7
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 42 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=21 | | Placebo N'=75 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 2 | 2.67 |
| G1WT+G2+P8WT | 0 | 0.00 | 2 | 2.67 |
| G1WT+P4 | 1 | 4.76 | 3 | 4.00 |
| G1WT+P8WT | 8 | 38.10 | 18 | 24.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.33 |
| G2+P4 | 10 | 47.62 | 37 | 49.33 |
| G2+P4+P8WT | 1 | 4.76 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.33 |
| G3+P8WT | 0 | 0.00 | 2 | 2.67 |
| G9+P8WT | 0 | 0.00 | 3 | 4.00 |
| GX | 0 | 0.00 | 1 | 1.33 |
| GX+P8WT | 0 | 0.00 | 5 | 6.67 |
| GX+PX | 1 | 4.76 | 0 | 0.00 |

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 severe RV GE episodes reported from 2 weeks after dose 2 of HRV vaccine or placebo up to visit 7
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 43 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | | HRV N' = 70 | | Placebo N' = 170 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.0 | - | 10.0 | - |
| | SD | 3.8 | - | 4.6 | - |
| | Median | 8.0 | - | 10.0 | - |
| | Minimum | 2.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 60 | 85.7 | 101 | 59.4 |
| | 5 | 7 | 10.0 | 28 | 16.5 |
| | more than 5 days | 3 | 4.3 | 41 | 24.1 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 7 | 10.0 | 19 | 11.2 |
| | 4 to 5 | 36 | 51.4 | 75 | 44.1 |
| | more than 5 | 27 | 38.6 | 76 | 44.7 |
| Duration of vomiting (days) | 0 day | 39 | 55.7 | 62 | 36.5 |
| | 1 day | 11 | 15.7 | 46 | 27.1 |
| | 2 days | 16 | 22.9 | 30 | 17.6 |
| | more than 2 days | 4 | 5.7 | 32 | 18.8 |
| Max number of episodes of vomiting /day | 0 | 39 | 55.7 | 62 | 36.5 |
| | 1 | 7 | 10.0 | 28 | 16.5 |
| | 2 to 4 | 22 | 31.4 | 62 | 36.5 |
| | more than 4 | 2 | 2.9 | 18 | 10.6 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 15 | 21.4 | 41 | 24.1 |
| | | | | | |
| | 36.6 to 37.9°C | 34 | 48.6 | 72 | 42.4 |
| | 38.0 to 38.4°C | 13 | 18.6 | 18 | 10.6 |
| | more than 38.4°C | 8 | 11.4 | 39 | 22.9 |
| Treatment | none | 37 | 52.9 | 72 | 42.4 |
| | rehydration | 29 | 41.4 | 77 | 45.3 |
| | hospitalization | 4 | 5.7 | 21 | 12.4 |
| Dehydration | none | 37 | 52.9 | 72 | 42.4 |
| | 1 to 5% | 13 | 18.6 | 18 | 10.6 |
| | more than 5 % | 20 | 28.6 | 80 | 47.1 |

N' = number of RV GE episodes reported in each group
n/% = number/percentage of specified symptom reported in each group among N'
Value= value of the considered parameter
SD= standard deviation
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5>5% dehydration)

## Table 44 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G1WT type (ATP cohort for efficacy)

| | | HRV N' = 22 | | Placebo N' = 47 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.8 | - | 11.2 | - |
| | SD | 4.0 | - | 4.4 | - |
| | Median | 9.5 | - | 11.0 | - |
| | Minimum | 2.0 | - | 3.0 | - |
| | Maximum | 16.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 21 | 95.5 | 24 | 51.1 |
| | 5 | 1 | 4.5 | 10 | 21.3 |
| | more than 5 days | 0 | 0.0 | 13 | 27.7 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 2 | 9.1 | 1 | 2.1 |
| | 4 to 5 | 9 | 40.9 | 28 | 59.6 |
| | more than 5 | 11 | 50.0 | 18 | 38.3 |
| Duration of vomiting (days) | 0 day | 12 | 54.5 | 12 | 25.5 |
| | 1 day | 2 | 9.1 | 15 | 31.9 |
| | 2 days | 6 | 27.3 | 11 | 23.4 |
| | more than 2 days | 2 | 9.1 | 9 | 19.1 |
| Max number of episodes of vomiting /day | 0 | 12 | 54.5 | 12 | 25.5 |
| | 1 | 2 | 9.1 | 9 | 19.1 |
| | 2 to 4 | 7 | 31.8 | 19 | 40.4 |
| | more than 4 | 1 | 4.5 | 7 | 14.9 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 3 | 13.6 | 9 | 19.1 |
| | 36.6 to 37.9°C | 8 | 36.4 | 20 | 42.6 |
| | 38.0 to 38.4°C | 7 | 31.8 | 6 | 12.8 |
| | more than 38.4°C | 4 | 18.2 | 12 | 25.5 |
| Treatment | none | 10 | 45.5 | 15 | 31.9 |
| | rehydration | 11 | 50.0 | 24 | 51.1 |
| | hospitalization | 1 | 4.5 | 8 | 17.0 |
| Dehydration | none | 10 | 45.5 | 15 | 31.9 |
| | 1 to 5% | 5 | 22.7 | 4 | 8.5 |
| | more than 5 % | 7 | 31.8 | 28 | 59.6 |

WT=Wild Type
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 45 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G2 type (ATP cohort for efficacy)**

| | | HRV N' = 42 | | Placebo N' = 107 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.8 | - | 9.5 | - |
| | SD | 3.8 | - | 4.7 | - |
| | Median | 8.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 36 | 85.7 | 66 | 61.7 |
| | 5 | 4 | 9.5 | 15 | 14.0 |
| | more than 5 days | 2 | 4.8 | 26 | 24.3 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 5 | 11.9 | 16 | 15.0 |
| | 4 to 5 | 22 | 52.4 | 42 | 39.3 |
| | more than 5 | 15 | 35.7 | 49 | 45.8 |
| Duration of vomiting (days) | 0 day | 23 | 54.8 | 42 | 39.3 |
| | 1 day | 8 | 19.0 | 30 | 28.0 |
| | 2 days | 9 | 21.4 | 17 | 15.9 |
| | more than 2 days | 2 | 4.8 | 18 | 16.8 |
| Max number of episodes of vomiting /day | 0 | 23 | 54.8 | 42 | 39.3 |
| | 1 | 4 | 9.5 | 15 | 14.0 |
| | 2 to 4 | 15 | 35.7 | 39 | 36.4 |
| | more than 4 | 0 | 0.0 | 11 | 10.3 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 11 | 26.2 | 29 | 27.1 |
| | 36.6 to 37.9°C | 20 | 47.6 | 43 | 40.2 |
| | 38.0 to 38.4°C | 7 | 16.7 | 12 | 11.2 |
| | more than 38.4°C | 4 | 9.5 | 23 | 21.5 |
| Treatment | none | 23 | 54.8 | 53 | 49.5 |
| | rehydration | 16 | 38.1 | 41 | 38.3 |
| | hospitalization | 3 | 7.1 | 13 | 12.1 |
| Dehydration | none | 23 | 54.8 | 53 | 49.5 |
| | 1 to 5% | 6 | 14.3 | 12 | 11.2 |
| | more than 5 % | 13 | 31.0 | 42 | 39.3 |

N' = number of RV GE episodes reported in each group
n/% = number/percentage of specified symptom reported in each group among N'
Value= value of the considered parameter
SD= standard deviation
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 46 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G3 type (ATP cohort for efficacy)

| | | HRV N' = 1 | | Placebo N' = 12 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 4.0 | - | 8.8 | - |
| | SD | 0.0 | - | 4.3 | - |
| | Median | 4.0 | - | 8.5 | - |
| | Minimum | 4.0 | - | 2.0 | - |
| | Maximum | 4.0 | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 8 | 66.7 |
| | 5 | 0 | 0.0 | 1 | 8.3 |
| | more than 5 days | 0 | 0.0 | 3 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 100 | 2 | 16.7 |
| | 4 to 5 | 0 | 0.0 | 6 | 50.0 |
| | more than 5 | 0 | 0.0 | 4 | 33.3 |
| Duration of vomiting (days) | 0 day | 0 | 0.0 | 5 | 41.7 |
| | 1 day | 1 | 100 | 2 | 16.7 |
| | 2 days | 0 | 0.0 | 4 | 33.3 |
| | more than 2 days | 0 | 0.0 | 1 | 8.3 |
| Max number of episodes of vomiting /day | 0 | 0 | 0.0 | 5 | 41.7 |
| | 1 | 1 | 100 | 4 | 33.3 |
| | 2 to 4 | 0 | 0.0 | 2 | 16.7 |
| | more than 4 | 0 | 0.0 | 1 | 8.3 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 100 | 4 | 33.3 |
| | 36.6 to 37.9°C | 0 | 0.0 | 5 | 41.7 |
| | 38.0 to 38.4°C | 0 | 0.0 | 1 | 8.3 |
| | more than 38.4°C | 0 | 0.0 | 2 | 16.7 |
| Treatment | none | 1 | 100 | 6 | 50.0 |
| | rehydration | 0 | 0.0 | 6 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 6 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 8.3 |
| | more than 5 % | 0 | 0.0 | 5 | 41.7 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 47 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G9 type (ATP cohort for efficacy)

| | | HRV N' = 1 | | Placebo N' = 5 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 4.0 | - | 10.6 | - |
| | SD | 0.0 | - | 4.0 | - |
| | Median | 4.0 | - | 12.0 | - |
| | Minimum | 4.0 | - | 5.0 | - |
| | Maximum | 4.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 3 | 60.0 |
| | 5 | 0 | 0.0 | 1 | 20.0 |
| | more than 5 days | 0 | 0.0 | 1 | 20.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 0 | 0.0 |
| | 4 to 5 | 1 | 100 | 3 | 60.0 |
| | more than 5 | 0 | 0.0 | 2 | 40.0 |
| Duration of vomiting (days) | 0 day | 1 | 100 | 2 | 40.0 |
| | 1 day | 0 | 0.0 | 1 | 20.0 |
| | 2 days | 0 | 0.0 | 2 | 40.0 |
| | more than 2 days | 0 | 0.0 | 0 | 0.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 100 | 2 | 40.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |
| | 2 to 4 | 0 | 0.0 | 3 | 60.0 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 0 | 0.0 |
| | 36.6 to 37.9°C | 1 | 100 | 4 | 80.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 1 | 20.0 |
| Treatment | none | 1 | 100 | 1 | 20.0 |
| | rehydration | 0 | 0.0 | 4 | 80.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 1 | 20.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 20.0 |
| | more than 5 % | 0 | 0.0 | 3 | 60.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 48 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By GX type (ATP cohort for efficacy)

| | | HRV N' = 6 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.7 | - | 13.4 | - |
| | SD | 2.6 | - | 3.5 | - |
| | Median | 7.0 | - | 14.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 50.0 | 5 | 62.5 |
| | 5 | 2 | 33.3 | 2 | 25.0 |
| | more than 5 days | 1 | 16.7 | 1 | 12.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 12.5 |
| | 4 to 5 | 4 | 66.7 | 1 | 12.5 |
| | more than 5 | 2 | 33.3 | 6 | 75.0 |
| Duration of vomiting (days) | 0 day | 4 | 66.7 | 1 | 12.5 |
| | 1 day | 1 | 16.7 | 2 | 25.0 |
| | 2 days | 1 | 16.7 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 5 | 62.5 |
| Max number of episodes of vomiting /day | 0 | 4 | 66.7 | 1 | 12.5 |
| | 1 | 1 | 16.7 | 1 | 12.5 |
| | 2 to 4 | 0 | 0.0 | 4 | 50.0 |
| | more than 4 | 1 | 16.7 | 2 | 25.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 16.7 | 1 | 12.5 |
| | 36.6 to 37.9°C | 5 | 83.3 | 4 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 3 | 37.5 |
| Treatment | none | 3 | 50.0 | 1 | 12.5 |
| | rehydration | 3 | 50.0 | 6 | 75.0 |
| | hospitalization | 0 | 0.0 | 1 | 12.5 |
| Dehydration | none | 3 | 50.0 | 1 | 12.5 |
| | 1 to 5% | 2 | 33.3 | 0 | 0.0 |
| | more than 5 % | 1 | 16.7 | 7 | 87.5 |

GX=G type unknown, but not vaccine strain
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 49 Characteristics of the GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | | HRV N' = 1168 | | Placebo N' = 1238 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.9 | - | 7.1 | - |
| | SD | 3.8 | - | 4.1 | - |
| | Median | 6.0 | - | 6.0 | - |
| | Minimum | 2.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 5 | 0.4 | 4 | 0.3 |
| | 1 to 4 days | 854 | 73.1 | 865 | 69.9 |
| | 5 | 120 | 10.3 | 135 | 10.9 |
| | more than 5 days | 189 | 16.2 | 234 | 18.9 |
| Maximum number of looser than normal stools/day | 0 | 5 | 0.4 | 4 | 0.3 |
| | 1 to 3 | 207 | 17.7 | 219 | 17.7 |
| | 4 to 5 | 620 | 53.1 | 655 | 52.9 |
| | more than 5 | 336 | 28.8 | 360 | 29.1 |
| Duration of vomiting (days) | 0 day | 831 | 71.1 | 848 | 68.5 |
| | 1 day | 169 | 14.5 | 189 | 15.3 |
| | 2 days | 99 | 8.5 | 100 | 8.1 |
| | more than 2 days | 69 | 5.9 | 101 | 8.2 |
| Max number of episodes of vomiting /day | 0 | 831 | 71.1 | 848 | 68.5 |
| | 1 | 113 | 9.7 | 134 | 10.8 |
| | 2 to 4 | 191 | 16.4 | 202 | 16.3 |
| | more than 4 | 33 | 2.8 | 54 | 4.4 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 398 | 34.1 | 434 | 35.1 |
| | 36.6 to 37.9°C | 584 | 50.0 | 603 | 48.7 |
| | 38.0 to 38.4°C | 73 | 6.3 | 73 | 5.9 |
| | more than 38.4°C | 113 | 9.7 | 128 | 10.3 |
| Treatment | none | 719 | 61.6 | 754 | 60.9 |
| | rehydration | 403 | 34.5 | 404 | 32.6 |
| | hospitalization | 46 | 3.9 | 80 | 6.5 |
| Dehydration | none | 719 | 61.6 | 754 | 60.9 |
| | 1 to 5% | 181 | 15.5 | 172 | 13.9 |
| | more than 5 % | 268 | 22.9 | 312 | 25.2 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 50 Duration (in years) of efficacy follow-up period - from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | HRV N = 1575 | Placebo N = 1573 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 2104 | 2087 |
| | Mean | 1.34 | 1.33 |
| | Minimum | 0.01 | 0.01 |
| | Q1 | 1.28 | 1.27 |
| | Median | 1.38 | 1.38 |
| | Q3 | 1.46 | 1.46 |
| | Maximum | 1.56 | 1.56 |

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

## 11.4.1. Vaccine efficacy from 2 weeks after Dose 2 up to Visit 7

### 11.4.1.1. Vaccine efficacy against severe RV GE

**Table 51 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 21 | 1.3 | 0.8 | 2.0 | 72.0 | 54.1 | 83.6 | <0.001 |
| Placebo | 1573 | 75 | 4.8 | 3.8 | 5.9 | - | - | - | - |

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

**Table 52 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Severity using Vesikari scale** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| ≥11 | HRV | 1575 | 21 | 1.3 | 0.8 | 2.0 | 72.0 | 54.1 | 83.6 | <0.001 |
| | Placebo | 1573 | 75 | 4.8 | 3.8 | 5.9 | - | - | - | - |
| ≥12 | HRV | 1575 | 15 | 1.0 | 0.5 | 1.6 | 78.0 | 61.1 | 88.3 | <0.001 |
| | Placebo | 1573 | 68 | 4.3 | 3.4 | 5.4 | - | - | - | - |
| ≥13 | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 86.0 | 70.5 | 94.2 | <0.001 |
| | Placebo | 1573 | 57 | 3.6 | 2.8 | 4.7 | - | - | - | - |
| ≥14 | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 83.0 | 63.7 | 93.1 | <0.001 |
| | Placebo | 1573 | 47 | 3.0 | 2.2 | 4.0 | - | - | - | - |
| ≥15 | HRV | 1575 | 4 | 0.3 | 0.1 | 0.6 | 89.2 | 69.9 | 97.2 | <0.001 |
| | Placebo | 1573 | 37 | 2.4 | 1.7 | 3.2 | - | - | - | - |
| ≥16 | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 92.6 | 70.6 | 99.1 | <0.001 |
| | Placebo | 1573 | 27 | 1.7 | 1.1 | 2.5 | - | - | - | - |
| ≥17 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 67.2 | 100.0 | <0.001 |
| | Placebo | 1573 | 13 | 0.8 | 0.4 | 1.4 | - | - | - | - |
| ≥18 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 49.4 | 100.0 | 0.004 |
| | Placebo | 1573 | 9 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| ≥19 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| =20 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode with a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.4.1.2. Vaccine efficacy against any RV GE

**Table 53 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 70 | 4.4 | 3.5 | 5.6 | 58.1 | 44.3 | 68.8 | <0.001 |
| Placebo | 1573 | 167 | 10.6 | 9.1 | 12.2 | - | - | - | - |

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

### 11.4.1.3. Vaccine efficacy by G and P types

**Table 54 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1575 | 9 | 0.6 | 0.3 | 1.1 | 64.0 | 20.4 | 85.2 | 0.009 |
| | Placebo | 1573 | 25 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| G2 | HRV | 1575 | 11 | 0.7 | 0.3 | 1.2 | 74.5 | 49.6 | 88.1 | <0.001 |
| | Placebo | 1573 | 43 | 2.7 | 2.0 | 3.7 | - | - | - | - |
| G3 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| G9 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| GX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 83.4 | -37.2 | 99.6 | 0.125 |
| | Placebo | 1573 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| P4 | HRV | 1575 | 12 | 0.8 | 0.4 | 1.3 | 72.1 | 46.2 | 86.6 | <0.001 |
| | Placebo | 1573 | 43 | 2.7 | 2.0 | 3.7 | - | - | - | - |
| P8WT | HRV | 1575 | 9 | 0.6 | 0.3 | 1.1 | 71.0 | 37.6 | 87.9 | <0.001 |
| | Placebo | 1573 | 31 | 2.0 | 1.3 | 2.8 | - | - | - | - |
| PX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 0.1 | -7739.7 | 98.7 | 1.000 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1 WT | HRV | 1575 | 12 | 0.8 | 0.4 | 1.3 | 77.8 | 58.0 | 89.2 | <0.001 |
| | Placebo | 1573 | 54 | 3.4 | 2.6 | 4.5 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 55 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 60.1 | 5.3 | 84.8 | 0.035 |
| | Placebo | 1573 | 20 | 1.3 | 0.8 | 2.0 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 80.0 | -78.5 | 99.6 | 0.218 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G2+P4 | HRV | 1575 | 11 | 0.7 | 0.3 | 1.2 | 72.5 | 45.5 | 87.3 | <0.001 |
| | Placebo | 1573 | 40 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| G9+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |

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

## Table 56 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 52.2 | 19.0 | 72.6 | 0.005 |
| | Placebo | 1573 | 46 | 2.9 | 2.1 | 3.9 | - | - | - | - |
| G2 | HRV | 1575 | 42 | 2.7 | 1.9 | 3.6 | 60.1 | 42.3 | 72.8 | <0.001 |
| | Placebo | 1573 | 105 | 6.7 | 5.5 | 8.0 | - | - | - | - |
| G3 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 91.7 | 43.7 | 99.8 | 0.003 |
| | Placebo | 1573 | 12 | 0.8 | 0.4 | 1.3 | - | - | - | - |
| G9 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 80.0 | -78.5 | 99.6 | 0.218 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| GX | HRV | 1575 | 6 | 0.4 | 0.1 | 0.8 | 25.1 | -146.2 | 78.6 | 0.789 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| P4 | HRV | 1575 | 43 | 2.7 | 2.0 | 3.7 | 59.9 | 42.3 | 72.5 | <0.001 |
| | Placebo | 1573 | 107 | 6.8 | 5.6 | 8.2 | - | - | - | - |
| P8WT | HRV | 1575 | 25 | 1.6 | 1.0 | 2.3 | 57.7 | 31.4 | 74.6 | <0.001 |
| | Placebo | 1573 | 59 | 3.8 | 2.9 | 4.8 | - | - | - | - |
| P9 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| PX | HRV | 1575 | 4 | 0.3 | 0.1 | 0.6 | -299.5 | -19574.0 | 60.5 | 0.376 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1575 | 49 | 3.1 | 2.3 | 4.1 | 62.1 | 46.9 | 73.3 | <0.001 |
| | Placebo | 1573 | 129 | 8.2 | 6.9 | 9.7 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 57 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1575 | 20 | 1.3 | 0.8 | 2.0 | 47.4 | 7.4 | 71.0 | 0.024 |
| | Placebo | 1573 | 38 | 2.4 | 1.7 | 3.3 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 77.8 | -7.2 | 97.7 | 0.065 |
| | Placebo | 1573 | 9 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| G2+P4 | HRV | 1575 | 42 | 2.7 | 1.9 | 3.6 | 58.9 | 40.5 | 72.0 | <0.001 |
| | Placebo | 1573 | 102 | 6.5 | 5.3 | 7.8 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 60.2 | 100.0 | <0.001 |
| | Placebo | 1573 | 11 | 0.7 | 0.3 | 1.2 | - | - | - | - |
| G9+P8WT | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 80.0 | -78.5 | 99.6 | 0.218 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |

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

## Table 58 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 70 | 2063.29 | 0.034 | 0.027 | 0.043 | 0.051 | 0.036 | 0.067 |
| Placebo | 1573 | 167 | 1966.79 | 0.085 | 0.073 | 0.099 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1575 | 22 | 2095.16 | 0.011 | 0.007 | 0.016 | 0.012 | 0.004 | 0.020 |
| Placebo | 1573 | 46 | 2061.90 | 0.022 | 0.017 | 0.030 | . | . | . |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | |
| HRV | 1575 | 49 | 2071.51 | 0.024 | 0.018 | 0.031 | 0.041 | 0.028 | 0.055 |
| Placebo | 1573 | 129 | 1987.90 | 0.065 | 0.055 | 0.077 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 21 | 2092.32 | 0.010 | 0.007 | 0.015 | 0.027 | 0.018 | 0.037 |
| Placebo | 1573 | 75 | 2038.88 | 0.037 | 0.029 | 0.046 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1575 | 9 | 2100.84 | 0.004 | 0.002 | 0.008 | 0.008 | 0.002 | 0.014 |
| Placebo | 1573 | 25 | 2074.80 | 0.012 | 0.008 | 0.018 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1575 | 12 | 2095.16 | 0.006 | 0.003 | 0.010 | 0.021 | 0.013 | 0.029 |
| Placebo | 1573 | 54 | 2048.62 | 0.026 | 0.020 | 0.034 | . | . | . |

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

**Table 59 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by Cox method (ATP cohort for efficacy)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 70 | 2063.29 | 0.03 | 0.03 | 0.04 | 60.00 | 47.12 | 69.74 | <0.001 |
| Placebo | 1573 | 167 | 1966.79 | 0.08 | 0.07 | 0.10 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1575 | 22 | 2095.16 | 0.01 | 0.01 | 0.02 | 53.15 | 22.13 | 71.81 | 0.003 |
| Placebo | 1573 | 46 | 2061.90 | 0.02 | 0.02 | 0.03 | - | - | - | - |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | | |
| HRV | 1575 | 49 | 2071.51 | 0.02 | 0.02 | 0.03 | 63.41 | 49.16 | 73.67 | <0.001 |
| Placebo | 1573 | 129 | 1987.90 | 0.06 | 0.05 | 0.08 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 21 | 2092.32 | 0.01 | 0.01 | 0.02 | 72.79 | 55.85 | 83.23 | <0.001 |
| Placebo | 1573 | 75 | 2038.88 | 0.04 | 0.03 | 0.05 | - | - | - | - |
| **Severe RVGE of G1WT** | | | | | | | | | | |
| HRV | 1575 | 9 | 2100.84 | 0.00 | 0.00 | 0.01 | 64.64 | 24.25 | 83.49 | 0.007 |
| Placebo | 1573 | 25 | 2074.80 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1WT** | | | | | | | | | | |
| HRV | 1575 | 12 | 2095.16 | 0.01 | 0.00 | 0.01 | 78.25 | 59.34 | 88.36 | <0.001 |
| Placebo | 1573 | 54 | 2048.62 | 0.03 | 0.02 | 0.03 | - | - | - | - |

WT=Wild type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)

### 11.4.1.4. Vaccine efficacy against hospitalisation due to RV GE

**Table 60 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 4 | 0.3 | 0.1 | 0.6 | 81.0 | 43.6 | 95.3 | <0.001 |
| Placebo | 1573 | 21 | 1.3 | 0.8 | 2.0 | - | - | - | - |

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

**Table 61 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 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 33 | 2.1 | 1.4 | 2.9 | 66.4 | 49.6 | 78.1 | <0.001 |
| Placebo | 1573 | 98 | 6.2 | 5.1 | 7.5 | - | - | - | - |

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

### 11.4.1.5. Vaccine efficacy against all cause GE

**Table 62 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 728 | 46.2 | 43.7 | 48.7 | 4.2 | -6.2 | 13.6 | 0.422 |
| Placebo | 1573 | 759 | 48.3 | 45.8 | 50.8 | - | - | - | - |

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

**Table 63 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 187 | 11.9 | 10.3 | 13.6 | 9.3 | -11.1 | 26.0 | 0.357 |
| Placebo | 1573 | 206 | 13.1 | 11.5 | 14.9 | - | - | - | - |

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

**Table 64 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 43 | 2.7 | 2.0 | 3.7 | 41.2 | 13.1 | 60.6 | 0.007 |
| Placebo | 1573 | 73 | 4.6 | 3.7 | 5.8 | - | - | - | - |

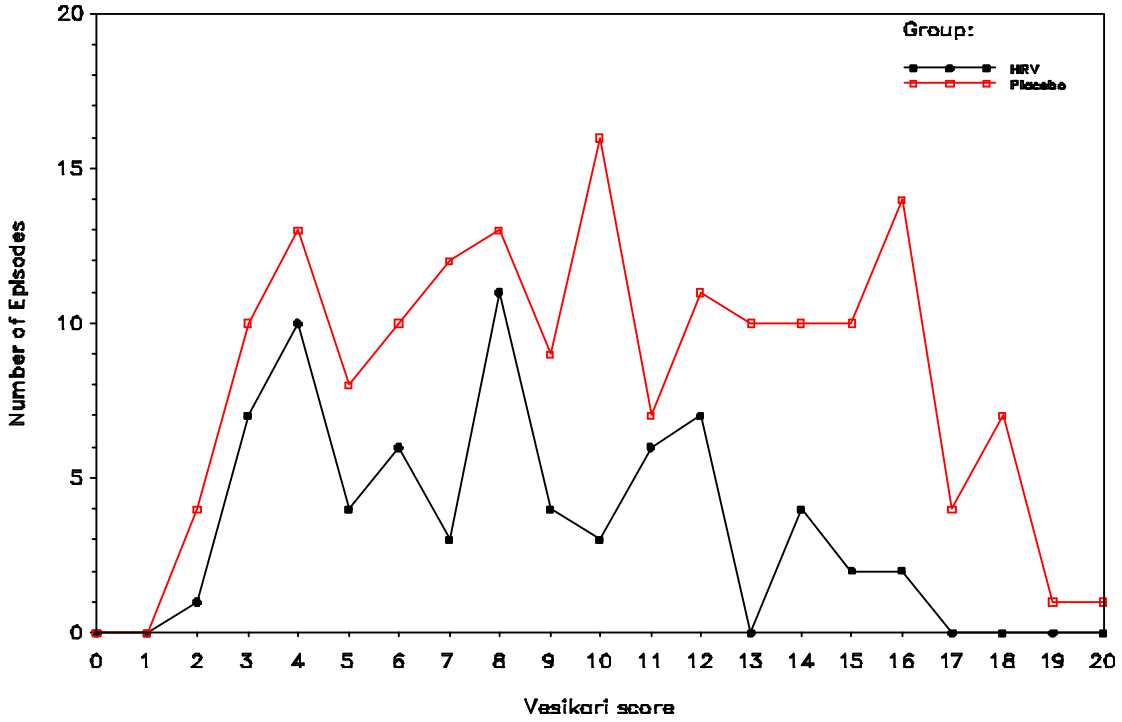
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 65 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 345 | 21.9 | 19.9 | 24.0 | 7.9 | -6.9 | 20.6 | 0.289 |
| Placebo | 1573 | 374 | 23.8 | 21.7 | 26.0 | - | - | - | - |

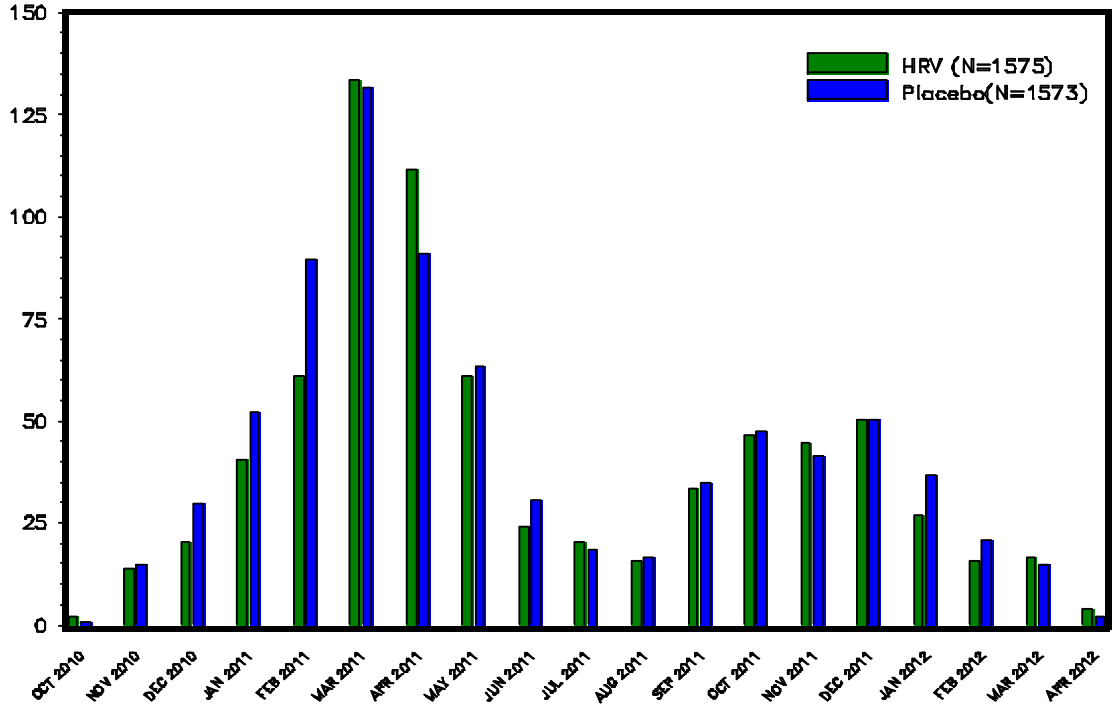
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 1 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



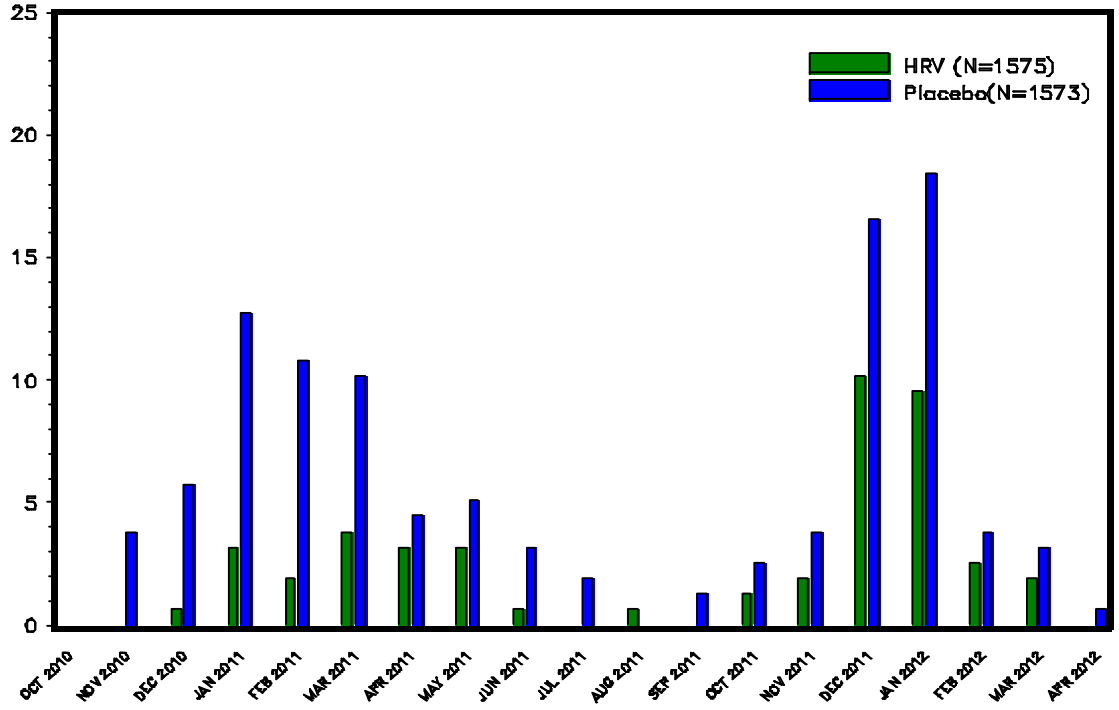

X axis = Score for each episodes computed based on the Vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 2** **Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 7 for HRV group and placebo group (ATP cohort for efficacy)**



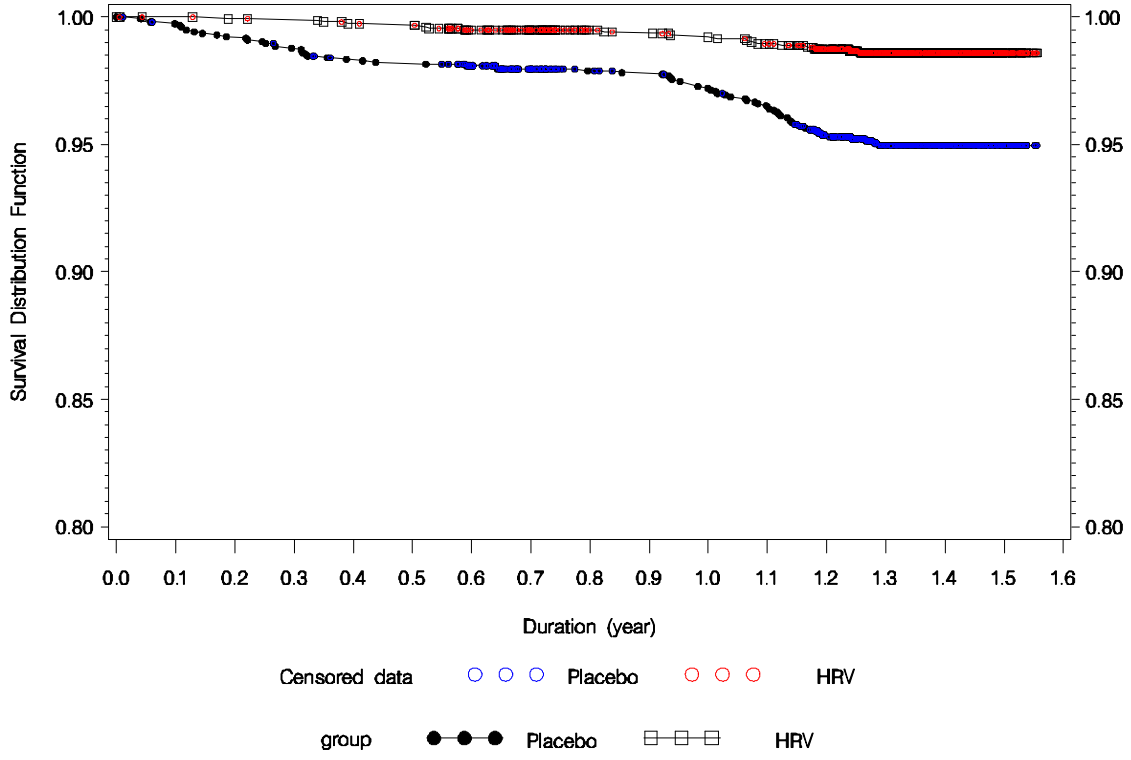

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 3** **Seasonal distribution of RVGE episodes reported from 2 weeks after Dose 2 up to Visit 7 for HRV group and placebo group (ATP cohort for efficacy)**



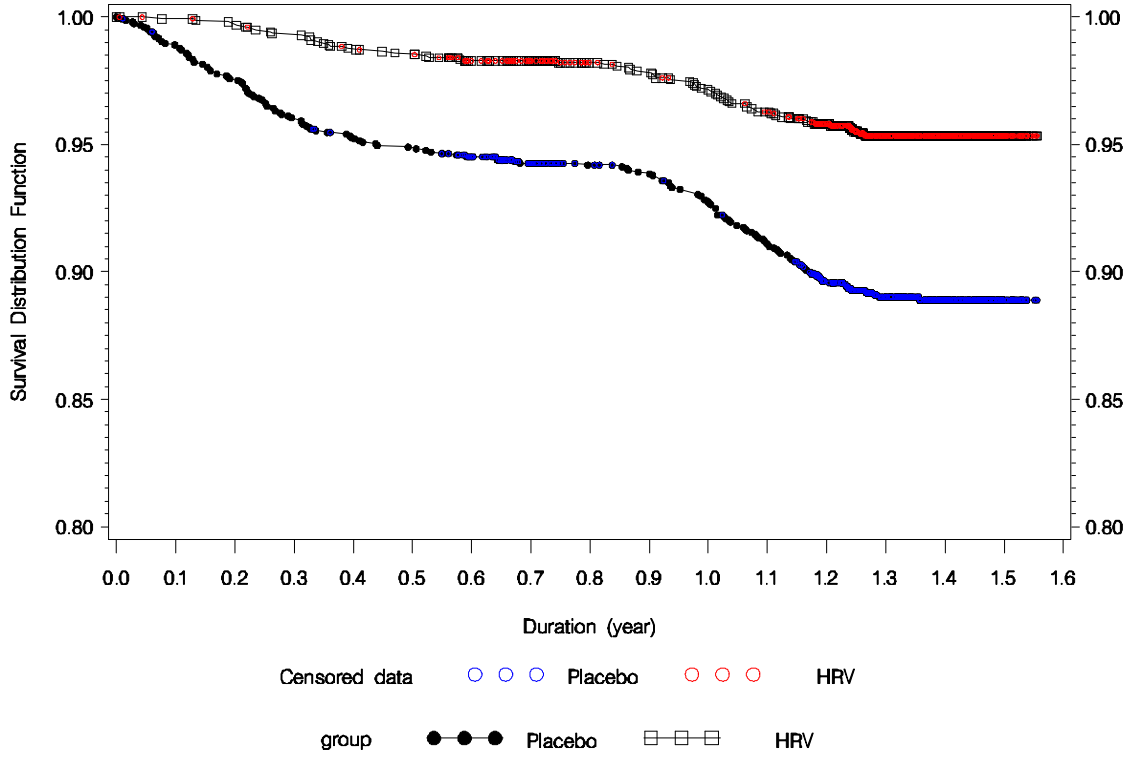

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 4** **The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



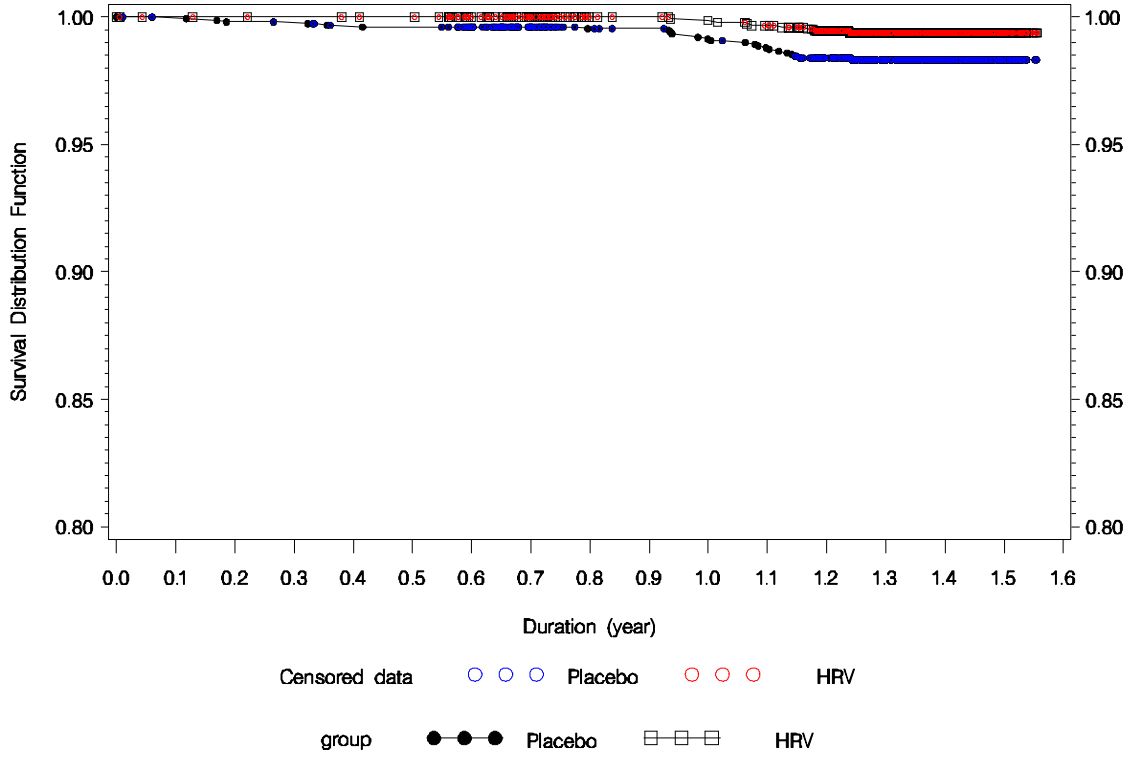

Y-axis has been cut at 0.8

**Figure 5** **The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



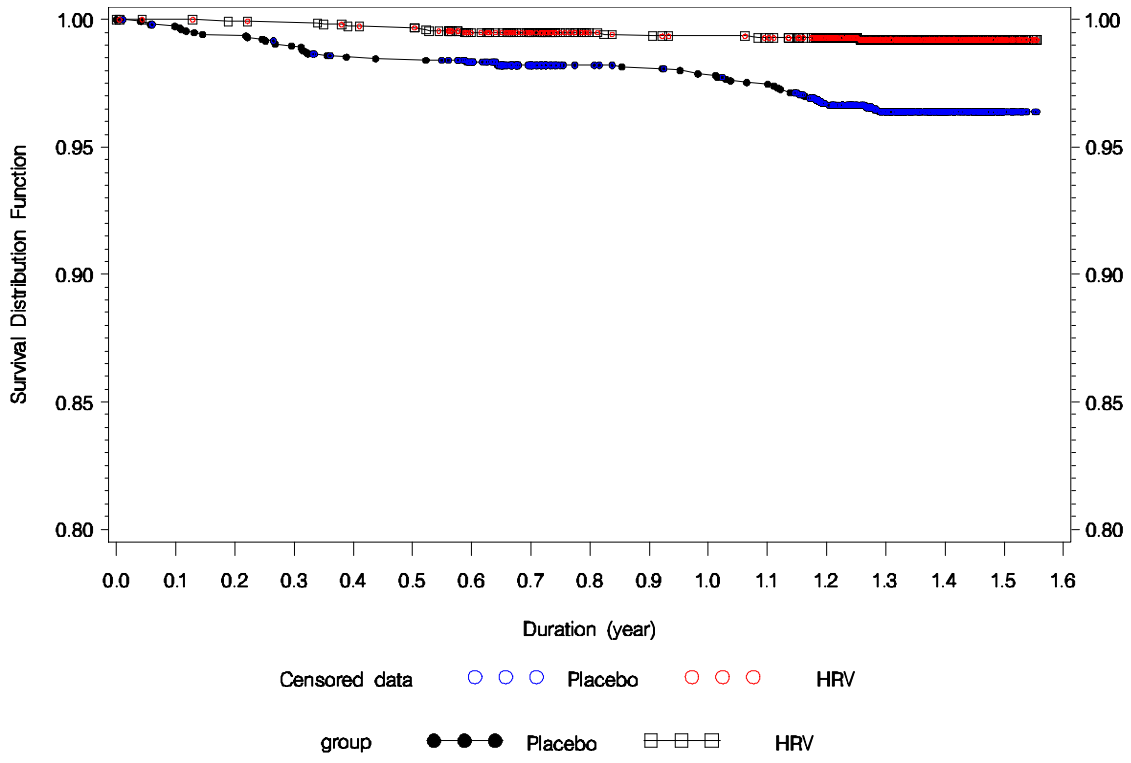

Y-axis has been cut at 0.8

**Figure 6** **The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



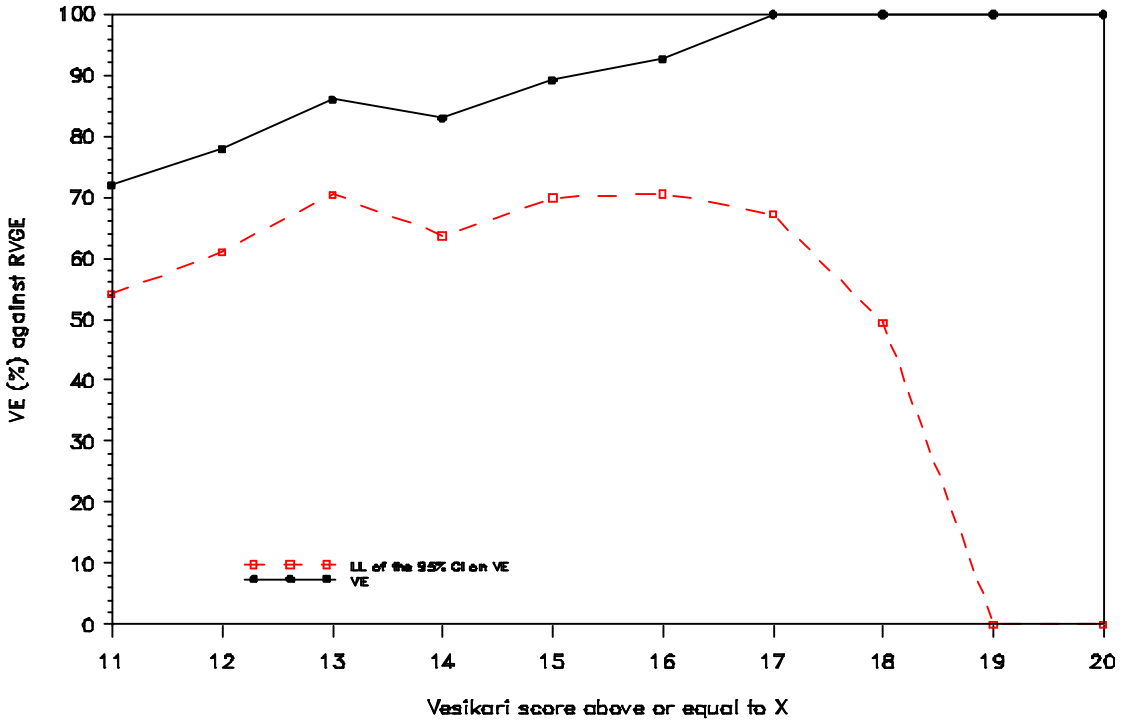

Y-axis has been cut at 0.8

**Figure 7** **The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



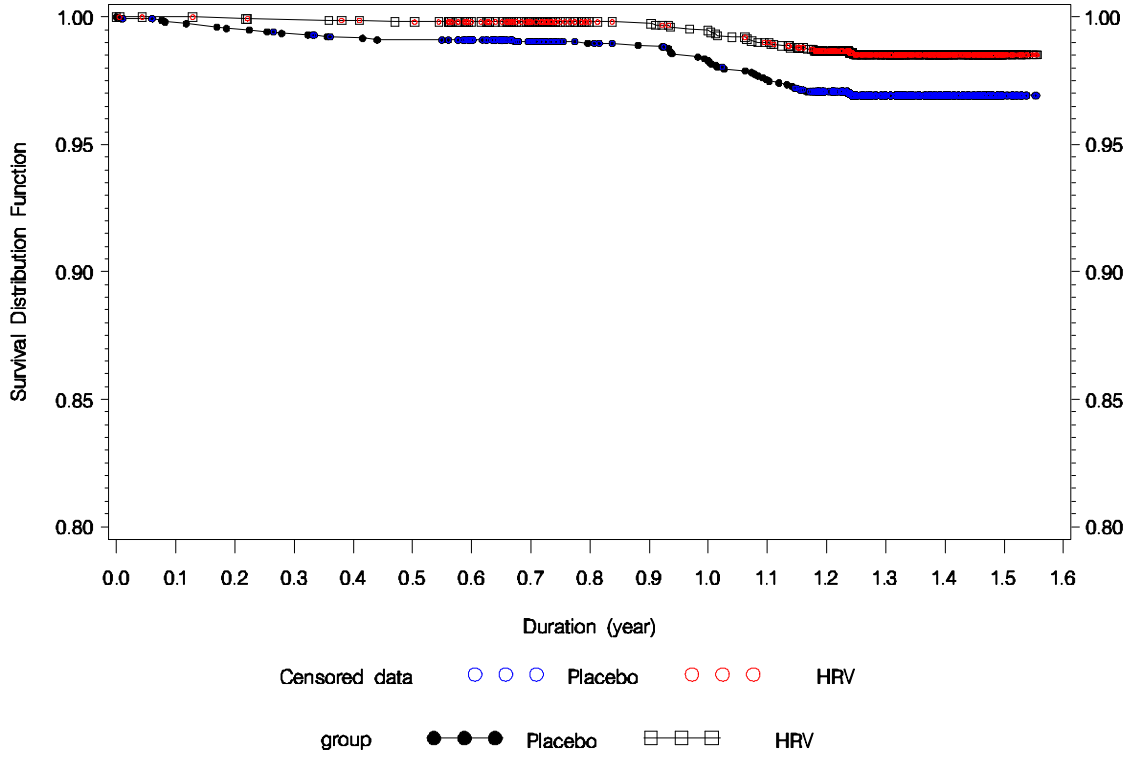

Y-axis has been cut at 0.8

**Figure 8** **Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from 2 weeks post dose 2 to visit 7 (ATP cohort for efficacy)**



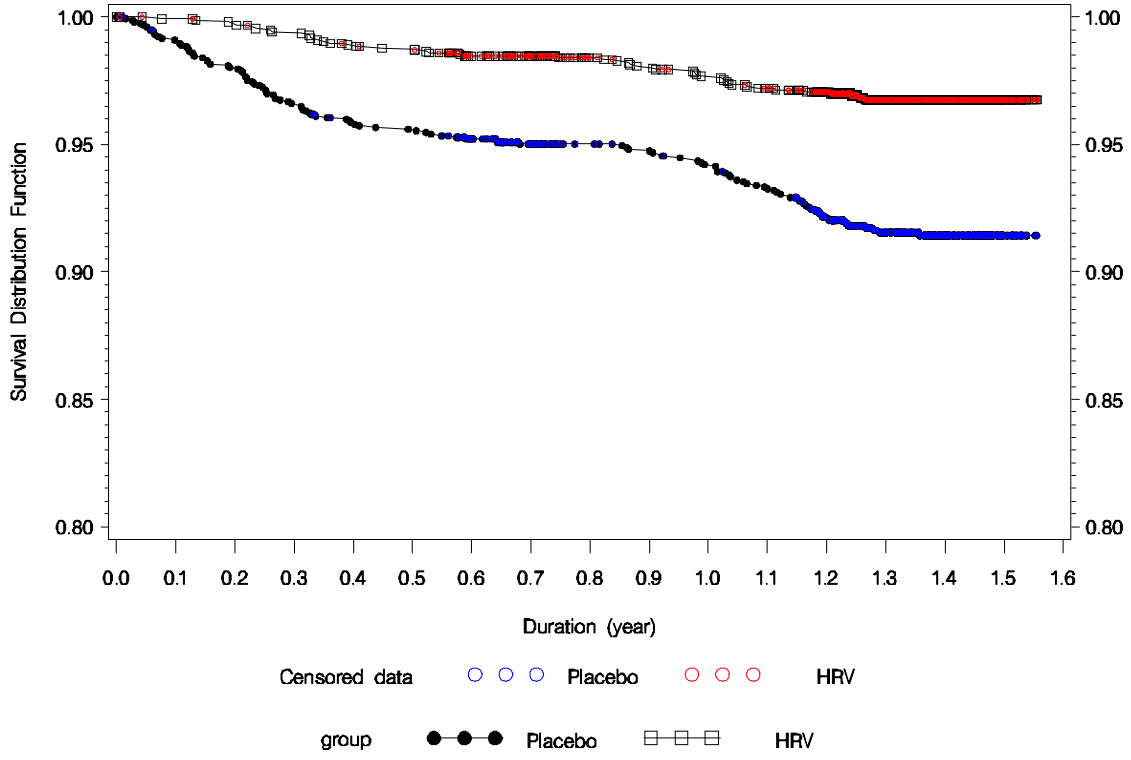

Y-axis has been cut at 0
X-axis has been cut at 11
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 9 The Kaplan Meier curve for any RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

**Figure 10 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

### 11.4.1.6. Characterization of GE episodes from 2 weeks after Dose 2 up to Visit 6

**Table 66 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | HRV N = 1575 | | Placebo N = 1573 | | Total N = 3148 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 997 | 63.3 | 956 | 60.8 | 1953 | 62.0 |
| | 1 | 425 | 27.0 | 452 | 28.7 | 877 | 27.9 |
| | 2 | 102 | 6.5 | 114 | 7.2 | 216 | 6.9 |
| | 3 | 38 | 2.4 | 31 | 2.0 | 69 | 2.2 |
| | 4 | 7 | 0.4 | 16 | 1.0 | 23 | 0.7 |
| | 5 | 5 | 0.3 | 3 | 0.2 | 8 | 0.3 |
| | 7 | 1 | 0.1 | 1 | 0.1 | 2 | 0.1 |
| | Any | 578 | 36.7 | 617 | 39.2 | 1195 | 38.0 |
| RVGE | 0 | 1548 | 98.3 | 1483 | 94.3 | 3031 | 96.3 |
| | 1 | 27 | 1.7 | 88 | 5.6 | 115 | 3.7 |
| | 2 | 0 | 0.0 | 2 | 0.1 | 2 | 0.1 |
| | Any | 27 | 1.7 | 90 | 5.7 | 117 | 3.7 |
| Severe GE | 0 | 1454 | 92.3 | 1453 | 92.4 | 2907 | 92.3 |
| | 1 | 113 | 7.2 | 109 | 6.9 | 222 | 7.1 |
| | 2 | 6 | 0.4 | 10 | 0.6 | 16 | 0.5 |
| | 3 | 2 | 0.1 | 1 | 0.1 | 3 | 0.1 |
| | Any | 121 | 7.7 | 120 | 7.6 | 241 | 7.7 |
| Severe RVGE | 0 | 1567 | 99.5 | 1541 | 98.0 | 3108 | 98.7 |
| | 1 | 8 | 0.5 | 32 | 2.0 | 40 | 1.3 |
| | Any | 8 | 0.5 | 32 | 2.0 | 40 | 1.3 |

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

**Table 67 Number of GE episodes reported from 2 weeks after Dose 2 up to Visit 6 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)**

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| **Event** | **Severity using 20 point Vesikari scale** | **n** | **%** | **n** | **%** |
| GE | Mild (1-6) | 451 | 56.2 | 499 | 58.1 |
| | Moderate (7-10) | 221 | 27.5 | 227 | 26.4 |
| | Severe (≥11) | 131 | 16.3 | 132 | 15.4 |
| | Unknown | 0 | 0.0 | 1 | 0.1 |
| | Any | 803 | 100 | 858 | 99.9 |
| RVGE | Mild (1-6) | 11 | 40.7 | 29 | 31.5 |
| | Moderate (7-10) | 8 | 29.6 | 31 | 33.7 |
| | Severe (≥11) | 8 | 29.6 | 32 | 34.8 |
| | Any | 27 | 100 | 92 | 100 |

HRV = HRV
Placebo = Placebo
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

## Table 68 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| | HRV N' = 803 | | Placebo N' = 859 | | Total N' = 1662 | |
|---|---|---|---|---|---|---|
| **Categories** | **n** | **%** | **n** | **%** | **n** | **%** |
| No stool results available | 46 | 5.7 | 48 | 5.6 | 94 | 5.7 |
| no stools collected | 46 | 5.7 | 48 | 5.6 | 94 | 5.7 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 69 Percentage of subjects with RV GE episodes from 2 weeks after Dose 2 up to Visit 6 by G and P type (ATP cohort for efficacy)

| Serotype | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| Any | 27 | 1.7 | 90 | 5.7 |
| G1 WT | 3 | 0.2 | 15 | 1.0 |
| G2 | 22 | 1.4 | 68 | 4.3 |
| G3 | 0 | 0.0 | 8 | 0.5 |
| G9 | 0 | 0.0 | 1 | 0.1 |
| GX | 2 | 0.1 | 2 | 0.1 |
| P4 | 22 | 1.4 | 67 | 4.3 |
| P8 WT | 3 | 0.2 | 23 | 1.5 |
| PX | 3 | 0.2 | 1 | 0.1 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 70 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 2 up to Visit 6 by G and P type (ATP cohort for efficacy)

| | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 8 | 0.5 | 32 | 2.0 |
| G1 WT | 0 | 0.0 | 6 | 0.4 |
| G2 | 7 | 0.4 | 27 | 1.7 |
| G3 | 0 | 0.0 | 2 | 0.1 |
| GX | 1 | 0.1 | 0 | 0.0 |
| P4 | 7 | 0.4 | 25 | 1.6 |
| P8 WT | 1 | 0.1 | 7 | 0.4 |
| PX | 1 | 0.1 | 1 | 0.1 |

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 severe RV GE episode whatever the serotype
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 71 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 6, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=27 | | Placebo N'=92 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 3 | 3.26 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 1.09 |
| G1WT+P8WT | 2 | 7.41 | 12 | 13.04 |
| G1WT+PX | 1 | 3.70 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.09 |
| G2+P4 | 21 | 77.78 | 64 | 69.57 |
| G2+P4+P8WT | 1 | 3.70 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.09 |
| G3+P8WT | 0 | 0.00 | 7 | 7.61 |
| G9+P8WT | 0 | 0.00 | 1 | 1.09 |
| GX | 0 | 0.00 | 1 | 1.09 |
| GX+P8WT | 0 | 0.00 | 1 | 1.09 |
| GX+PX | 2 | 7.41 | 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 2 of HRV vaccine or placebo up to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 72 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to Visit 6, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=8 | | Placebo N'=32 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 3.13 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 3.13 |
| G1WT+P8WT | 0 | 0.00 | 4 | 12.50 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 3.13 |
| G2+P4 | 6 | 75.00 | 23 | 71.88 |
| G2+P4+P8WT | 1 | 12.50 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 3.13 |
| G3+P8WT | 0 | 0.00 | 1 | 3.13 |
| GX+PX | 1 | 12.50 | 0 | 0.00 |

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 severe RV GE episodes reported from 2 weeks after dose 2 of HRV vaccine or placebo up to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 73 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| | | HRV N' = 27 | | Placebo N' = 92 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.0 | - | 8.9 | - |
| | SD | 4.0 | - | 4.3 | - |
| | Median | 8.0 | - | 8.5 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 22 | 81.5 | 57 | 62.0 |
| | 5 | 3 | 11.1 | 13 | 14.1 |
| | more than 5 days | 2 | 7.4 | 22 | 23.9 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 4 | 14.8 | 14 | 15.2 |
| | 4 to 5 | 11 | 40.7 | 36 | 39.1 |
| | more than 5 | 12 | 44.4 | 42 | 45.7 |
| Duration of vomiting (days) | 0 day | 16 | 59.3 | 45 | 48.9 |
| | 1 day | 4 | 14.8 | 19 | 20.7 |
| | 2 days | 5 | 18.5 | 13 | 14.1 |
| | more than 2 days | 2 | 7.4 | 15 | 16.3 |
| Max number of episodes of vomiting /day | 0 | 16 | 59.3 | 45 | 48.9 |
| | 1 | 2 | 7.4 | 12 | 13.0 |
| | 2 to 4 | 8 | 29.6 | 27 | 29.3 |
| | more than 4 | 1 | 3.7 | 8 | 8.7 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 6 | 22.2 | 30 | 32.6 |
| | 36.6 to 37.9°C | 13 | 48.1 | 40 | 43.5 |
| | 38.0 to 38.4°C | 6 | 22.2 | 12 | 13.0 |
| | more than 38.4°C | 2 | 7.4 | 10 | 10.9 |
| Treatment | none | 15 | 55.6 | 46 | 50.0 |
| | rehydration | 10 | 37.0 | 32 | 34.8 |
| | hospitalization | 2 | 7.4 | 14 | 15.2 |
| Dehydration | none | 15 | 55.6 | 46 | 50.0 |
| | 1 to 5% | 3 | 11.1 | 11 | 12.0 |
| | more than 5 % | 9 | 33.3 | 35 | 38.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 74 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By G1WT type (ATP cohort for efficacy)

| | | HRV N' = 3 | | Placebo N' = 16 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.0 | - | 8.6 | - |
| | SD | 3.6 | - | 3.4 | - |
| | Median | 5.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 3.0 | - |
| | Maximum | 10.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 100 | 10 | 62.5 |
| | 5 | 0 | 0.0 | 4 | 25.0 |
| | more than 5 days | 0 | 0.0 | 2 | 12.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 33.3 | 0 | 0.0 |
| | 4 to 5 | 1 | 33.3 | 11 | 68.8 |
| | more than 5 | 1 | 33.3 | 5 | 31.3 |
| Duration of vomiting (days) | 0 day | 3 | 100 | 8 | 50.0 |
| | 1 day | 0 | 0.0 | 5 | 31.3 |
| | 2 days | 0 | 0.0 | 2 | 12.5 |
| | more than 2 days | 0 | 0.0 | 1 | 6.3 |
| Max number of episodes of vomiting /day | 0 | 3 | 100 | 8 | 50.0 |
| | 1 | 0 | 0.0 | 2 | 12.5 |
| | 2 to 4 | 0 | 0.0 | 6 | 37.5 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 4 | 25.0 |
| | 36.6 to 37.9°C | 1 | 33.3 | 8 | 50.0 |
| | 38.0 to 38.4°C | 1 | 33.3 | 3 | 18.8 |
| | more than 38.4°C | 1 | 33.3 | 1 | 6.3 |
| Treatment | none | 2 | 66.7 | 8 | 50.0 |
| | rehydration | 1 | 33.3 | 4 | 25.0 |
| | hospitalization | 0 | 0.0 | 4 | 25.0 |
| Dehydration | none | 2 | 66.7 | 8 | 50.0 |
| | 1 to 5% | 1 | 33.3 | 2 | 12.5 |
| | more than 5 % | 0 | 0.0 | 6 | 37.5 |

WT =Wild Type
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 75 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By G2 type (ATP cohort for efficacy)

| | | HRV N' = 22 | | Placebo N' = 70 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.2 | - | 9.2 | - |
| | SD | 4.0 | - | 4.6 | - |
| | Median | 8.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 19 | 86.4 | 42 | 60.0 |
| | 5 | 2 | 9.1 | 8 | 11.4 |
| | more than 5 days | 1 | 4.5 | 20 | 28.6 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 3 | 13.6 | 12 | 17.1 |
| | 4 to 5 | 9 | 40.9 | 25 | 35.7 |
| | more than 5 | 10 | 45.5 | 33 | 47.1 |
| Duration of vomiting (days) | 0 day | 12 | 54.5 | 33 | 47.1 |
| | 1 day | 4 | 18.2 | 14 | 20.0 |
| | 2 days | 4 | 18.2 | 11 | 15.7 |
| | more than 2 days | 2 | 9.1 | 12 | 17.1 |
| Max number of episodes of vomiting /day | 0 | 12 | 54.5 | 33 | 47.1 |
| | 1 | 2 | 9.1 | 6 | 8.6 |
| | 2 to 4 | 8 | 36.4 | 23 | 32.9 |
| | more than 4 | 0 | 0.0 | 8 | 11.4 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 6 | 27.3 | 22 | 31.4 |
| | 36.6 to 37.9°C | 10 | 45.5 | 29 | 41.4 |
| | 38.0 to 38.4°C | 5 | 22.7 | 10 | 14.3 |
| | more than 38.4°C | 1 | 4.5 | 9 | 12.9 |
| Treatment | none | 11 | 50.0 | 35 | 50.0 |
| | rehydration | 9 | 40.9 | 24 | 34.3 |
| | hospitalization | 2 | 9.1 | 11 | 15.7 |
| Dehydration | none | 11 | 50.0 | 35 | 50.0 |
| | 1 to 5% | 2 | 9.1 | 7 | 10.0 |
| | more than 5 % | 9 | 40.9 | 28 | 40.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 76 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By G3 type (ATP cohort for efficacy)**

| | | HRV N' = 0 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | - | - | 8.8 | - |
| | SD | - | - | 4.2 | - |
| | Median | - | - | 8.5 | - |
| | Minimum | - | - | 2.0 | - |
| | Maximum | - | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | - | - | 0 | 0.0 |
| | 1 to 4 days | - | - | 5 | 62.5 |
| | 5 | - | - | 1 | 12.5 |
| | more than 5 days | - | - | 2 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | - | - | 0 | 0.0 |
| | 1 to 3 | - | - | 1 | 12.5 |
| | 4 to 5 | - | - | 4 | 50.0 |
| | more than 5 | - | - | 3 | 37.5 |
| Duration of vomiting (days) | 0 day | - | - | 3 | 37.5 |
| | 1 day | - | - | 2 | 25.0 |
| | 2 days | - | - | 2 | 25.0 |
| | more than 2 days | - | - | 1 | 12.5 |
| Max number of episodes of vomiting /day | 0 | - | - | 3 | 37.5 |
| | 1 | - | - | 3 | 37.5 |
| | 2 to 4 | - | - | 1 | 12.5 |
| | more than 4 | - | - | 1 | 12.5 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | - | - | 3 | 37.5 |
| | 36.6 to 37.9°C | - | - | 4 | 50.0 |
| | 38.0 to 38.4°C | - | - | 0 | 0.0 |
| | more than 38.4°C | - | - | 1 | 12.5 |
| Treatment | none | - | - | 4 | 50.0 |
| | rehydration | - | - | 4 | 50.0 |
| | hospitalization | - | - | 0 | 0.0 |
| Dehydration | none | - | - | 4 | 50.0 |
| | 1 to 5% | - | - | 1 | 12.5 |
| | more than 5 % | - | - | 3 | 37.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 77 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By GX type (ATP cohort for efficacy)

| | | HRV N' = 2 | | Placebo N' = 2 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.5 | - | 9.0 | - |
| | SD | 4.9 | - | 1.4 | - |
| | Median | 8.5 | - | 9.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 10.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 0 | 0.0 | 2 | 100 |
| | 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 days | 1 | 50.0 | 0 | 0.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 50.0 |
| | 4 to 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 | 1 | 50.0 | 1 | 50.0 |
| Duration of vomiting (days) | 0 day | 1 | 50.0 | 0 | 0.0 |
| | 1 day | 0 | 0.0 | 1 | 50.0 |
| | 2 days | 1 | 50.0 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 1 | 50.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 50.0 | 0 | 0.0 |
| | 1 | 0 | 0.0 | 1 | 50.0 |
| | 2 to 4 | 0 | 0.0 | 1 | 50.0 |
| | more than 4 | 1 | 50.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 1 | 50.0 |
| | 36.6 to 37.9°C | 2 | 100 | 1 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 0 | 0.0 |
| Treatment | none | 2 | 100 | 1 | 50.0 |
| | rehydration | 0 | 0.0 | 1 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 2 | 100 | 1 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 0 | 0.0 |
| | more than 5 % | 0 | 0.0 | 1 | 50.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain

## Table 78 Characteristics of the GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| | | HRV N' = 803 | | Placebo N' = 859 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.6 | - | 6.5 | - |
| | SD | 3.7 | - | 3.7 | - |
| | Median | 6.0 | - | 6.0 | - |
| | Minimum | 2.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 3 | 0.4 | 2 | 0.2 |
| | 1 to 4 days | 573 | 71.4 | 601 | 70.0 |
| | 5 | 84 | 10.5 | 78 | 9.1 |
| | more than 5 days | 143 | 17.8 | 178 | 20.7 |
| Maximum number of looser than normal stools/day | 0 | 3 | 0.4 | 2 | 0.2 |
| | 1 to 3 | 168 | 20.9 | 156 | 18.2 |
| | 4 to 5 | 406 | 50.6 | 463 | 53.9 |
| | more than 5 | 226 | 28.1 | 238 | 27.7 |
| Duration of vomiting (days) | 0 day | 607 | 75.6 | 650 | 75.7 |
| | 1 day | 93 | 11.6 | 107 | 12.5 |
| | 2 days | 58 | 7.2 | 48 | 5.6 |
| | more than 2 days | 45 | 5.6 | 54 | 6.3 |
| Max number of episodes of vomiting /day | 0 | 607 | 75.6 | 650 | 75.7 |
| | 1 | 66 | 8.2 | 79 | 9.2 |
| | 2 to 4 | 114 | 14.2 | 107 | 12.5 |
| | more than 4 | 16 | 2.0 | 23 | 2.7 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 309 | 38.5 | 352 | 41.0 |
| | 36.6 to 37.9°C | 373 | 46.5 | 378 | 44.0 |
| | 38.0 to 38.4°C | 49 | 6.1 | 54 | 6.3 |
| | more than 38.4°C | 72 | 9.0 | 75 | 8.7 |
| Treatment | none | 518 | 64.5 | 568 | 66.1 |
| | rehydration | 245 | 30.5 | 240 | 27.9 |
| | hospitalization | 40 | 5.0 | 51 | 5.9 |
| Dehydration | none | 518 | 64.5 | 568 | 66.1 |
| | 1 to 5% | 112 | 13.9 | 115 | 13.4 |
| | more than 5 % | 173 | 21.5 | 176 | 20.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 79 Duration (in years) of efficacy follow-up period - from 2 weeks after Dose 2 up to visit 6 (ATP cohort for efficacy)**

| | | HRV N = 1575 | Placebo N = 1573 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 1068 | 1063 |
| | Mean | 0.68 | 0.68 |
| | Minimum | 0.01 | 0.01 |
| | Q1 | 0.64 | 0.64 |
| | Median | 0.68 | 0.68 |
| | Q3 | 0.73 | 0.72 |
| | Maximum | 0.93 | 0.93 |

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

## 11.4.2. Vaccine efficacy from 2 weeks after Dose 2 up to Visit 6

### 11.4.2.1. Vaccine efficacy against severe RV GE

**Table 80 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 75.0 | 44.7 | 90.1 | <0.001 |
| Placebo | 1573 | 32 | 2.0 | 1.4 | 2.9 | - | - | - | - |

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

**Table 81 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Severity using Vesikari scale | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| ≥11 | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 75.0 | 44.7 | 90.1 | <0.001 |
| | Placebo | 1573 | 32 | 2.0 | 1.4 | 2.9 | - | - | - | - |
| ≥12 | HRV | 1575 | 6 | 0.4 | 0.1 | 0.8 | 78.6 | 47.3 | 92.8 | <0.001 |
| | Placebo | 1573 | 28 | 1.8 | 1.2 | 2.6 | - | - | - | - |
| ≥13 | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 85.0 | 49.5 | 97.1 | <0.001 |
| | Placebo | 1573 | 20 | 1.3 | 0.8 | 2.0 | - | - | - | - |
| ≥14 | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 77.0 | 16.1 | 95.8 | 0.021 |
| | Placebo | 1573 | 13 | 0.8 | 0.4 | 1.4 | - | - | - | - |
| ≥15 | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 77.8 | -7.2 | 97.7 | 0.065 |
| | Placebo | 1573 | 9 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| ≥16 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 87.5 | 6.9 | 99.7 | 0.039 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| ≥17 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -51.3 | 100.0 | 0.125 |
| | Placebo | 1573 | 4 | 0.3 | 0.1 | 0.6 | - | - | - | - |
| ≥18 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| ≥19 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| =20 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode with a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.4.2.2. Vaccine efficacy against any RV GE

**Table 82 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 27 | 1.7 | 1.1 | 2.5 | 70.0 | 53.5 | 81.3 | <0.001 |
| Placebo | 1573 | 90 | 5.7 | 4.6 | 7.0 | - | - | - | - |

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

### 11.4.2.3. Vaccine efficacy by G and P types

**Table 83 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by RV type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 15.2 | 100.0 | 0.031 |
| | Placebo | 1573 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| G2 | HRV | 1575 | 7 | 0.4 | 0.2 | 0.9 | 74.1 | 39.1 | 90.5 | <0.001 |
| | Placebo | 1573 | 27 | 1.7 | 1.1 | 2.5 | - | - | - | - |
| G3 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| GX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | Und. | Und. | Und. | 1.000 |
| | Placebo | 1573 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |
| P4 | HRV | 1575 | 7 | 0.4 | 0.2 | 0.9 | 72.0 | 33.5 | 89.8 | 0.002 |
| | Placebo | 1573 | 25 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| P8WT | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 85.7 | -11.1 | 99.7 | 0.070 |
| | Placebo | 1573 | 7 | 0.4 | 0.2 | 0.9 | - | - | - | - |
| PX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 0.1 | -7739.7 | 98.7 | 1.000 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 71.5 | 35.7 | 88.8 | 0.001 |
| | Placebo | 1573 | 28 | 1.8 | 1.2 | 2.6 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain
Und. = cannot be estimated

**Table 84 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by combination of G and P type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -9.0 | 100.0 | 0.062 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| G2+P4 | HRV | 1575 | 7 | 0.4 | 0.2 | 0.9 | 72.0 | 33.5 | 89.8 | 0.002 |
| | Placebo | 1573 | 25 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |

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

## Table 85 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by RV type (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 80.0 | 29.4 | 96.3 | 0.007 |
| | Placebo | 1573 | 15 | 1.0 | 0.5 | 1.6 | - | - | - | - |
| G2 | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 67.7 | 47.1 | 81.0 | <0.001 |
| | Placebo | 1573 | 68 | 4.3 | 3.4 | 5.4 | - | - | - | - |
| G3 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 41.5 | 100.0 | 0.008 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| G9 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| GX | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 0.1 | -1277.8 | 92.8 | 1.000 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| P4 | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 67.2 | 46.2 | 80.7 | <0.001 |
| | Placebo | 1573 | 67 | 4.3 | 3.3 | 5.4 | - | - | - | - |
| P8WT | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 87.0 | 56.9 | 97.5 | <0.001 |
| | Placebo | 1573 | 23 | 1.5 | 0.9 | 2.2 | - | - | - | - |
| PX | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | -199.6 | -15629.2 | 75.9 | 0.626 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1575 | 24 | 1.5 | 1.0 | 2.3 | 69.3 | 50.9 | 81.4 | <0.001 |
| | Placebo | 1573 | 78 | 5.0 | 3.9 | 6.2 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 86 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by combination of G and P types (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 84.6 | 32.1 | 98.3 | 0.007 |
| | Placebo | 1573 | 13 | 0.8 | 0.4 | 1.4 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| G2+P4 | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 67.2 | 46.2 | 80.7 | <0.001 |
| | Placebo | 1573 | 67 | 4.3 | 3.3 | 5.4 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 41.5 | 100.0 | 0.008 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| G9+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |

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

## Table 87 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 27 | 1058.48 | 0.026 | 0.017 | 0.037 | 0.062 | 0.042 | 0.084 |
| Placebo | 1573 | 90 | 1025.32 | 0.088 | 0.071 | 0.108 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1575 | 3 | 1066.78 | 0.003 | 0.001 | 0.009 | 0.011 | 0.003 | 0.021 |
| Placebo | 1573 | 15 | 1056.32 | 0.014 | 0.009 | 0.024 | . | . | . |
| **Any RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1575 | 24 | 1059.46 | 0.023 | 0.015 | 0.034 | 0.053 | 0.034 | 0.073 |
| Placebo | 1573 | 78 | 1030.71 | 0.076 | 0.061 | 0.094 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.008 | 0.004 | 0.015 | 0.023 | 0.011 | 0.036 |
| Placebo | 1573 | 32 | 1050.22 | 0.030 | 0.022 | 0.043 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1575 | 0 | 1067.76 | 0 | Und. | Und. | 0.006 | Und. | Und. |
| Placebo | 1573 | 6 | 1060.24 | 0.006 | 0.003 | 0.013 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.008 | 0.004 | 0.015 | 0.019 | 0.008 | 0.032 |
| Placebo | 1573 | 28 | 1052.01 | 0.027 | 0.018 | 0.039 | . | . | . |

WT=Wild Type
N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(S) in each group
T(Year)= Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Risk difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner
Und. = cannot be estimated

**Table 88 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by Cox method (ATP cohort for efficacy)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 27 | 1058.48 | 0.03 | 0.02 | 0.04 | 70.79 | 55.09 | 81.00 | <0.001 |
| Placebo | 1573 | 90 | 1025.32 | 0.09 | 0.07 | 0.11 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1575 | 3 | 1066.78 | 0.00 | 0.00 | 0.01 | 80.15 | 31.45 | 94.25 | 0.011 |
| Placebo | 1573 | 15 | 1056.32 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Any RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1575 | 24 | 1059.46 | 0.02 | 0.02 | 0.03 | 69.92 | 52.46 | 80.96 | <0.001 |
| Placebo | 1573 | 78 | 1030.71 | 0.08 | 0.06 | 0.09 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.01 | 0.00 | 0.02 | 75.27 | 46.34 | 88.60 | <0.001 |
| Placebo | 1573 | 32 | 1050.22 | 0.03 | 0.02 | 0.04 | - | - | - | - |
| **Severe RVGE of G1 WT** | | | | | | | | | | |
| HRV | 1575 | 0 | 1067.76 | 0.00 | Und. | Und. | 100.00 | Und. | 100.00 | 0.994 |
| Placebo | 1573 | 6 | 1060.24 | 0.01 | 0.00 | 0.01 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.01 | 0.00 | 0.02 | 71.70 | 37.90 | 87.10 | 0.002 |
| Placebo | 1573 | 28 | 1052.01 | 0.03 | 0.02 | 0.04 | - | - | - | - |

WT=Wild Type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)
Und. = cannot be estimated

### 11.4.2.4. Vaccine efficacy against hospitalisation due to RV

**Table 89 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 85.7 | 37.9 | 98.4 | 0.004 |
| Placebo | 1573 | 14 | 0.9 | 0.5 | 1.5 | - | - | - | - |

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

**Table 90 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 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 12 | 0.8 | 0.4 | 1.3 | 73.9 | 50.0 | 87.4 | <0.001 |
| Placebo | 1573 | 46 | 2.9 | 2.1 | 3.9 | - | - | - | - |

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

### 11.4.2.5. Vaccine efficacy against all cause GE and severe GE

**Table 91 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 578 | 36.7 | 34.3 | 39.1 | 6.4 | -5.0 | 16.6 | 0.262 |
| Placebo | 1573 | 617 | 39.2 | 36.8 | 41.7 | - | - | - | - |

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

**Table 92 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 121 | 7.7 | 6.4 | 9.1 | -0.7 | -30.7 | 22.4 | 1.000 |
| Placebo | 1573 | 120 | 7.6 | 6.4 | 9.1 | - | - | - | - |

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

## Table 93 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 37 | 2.3 | 1.7 | 3.2 | 21.4 | -23.6 | 50.3 | 0.323 |
| Placebo | 1573 | 47 | 3.0 | 2.2 | 4.0 | - | - | - | - |

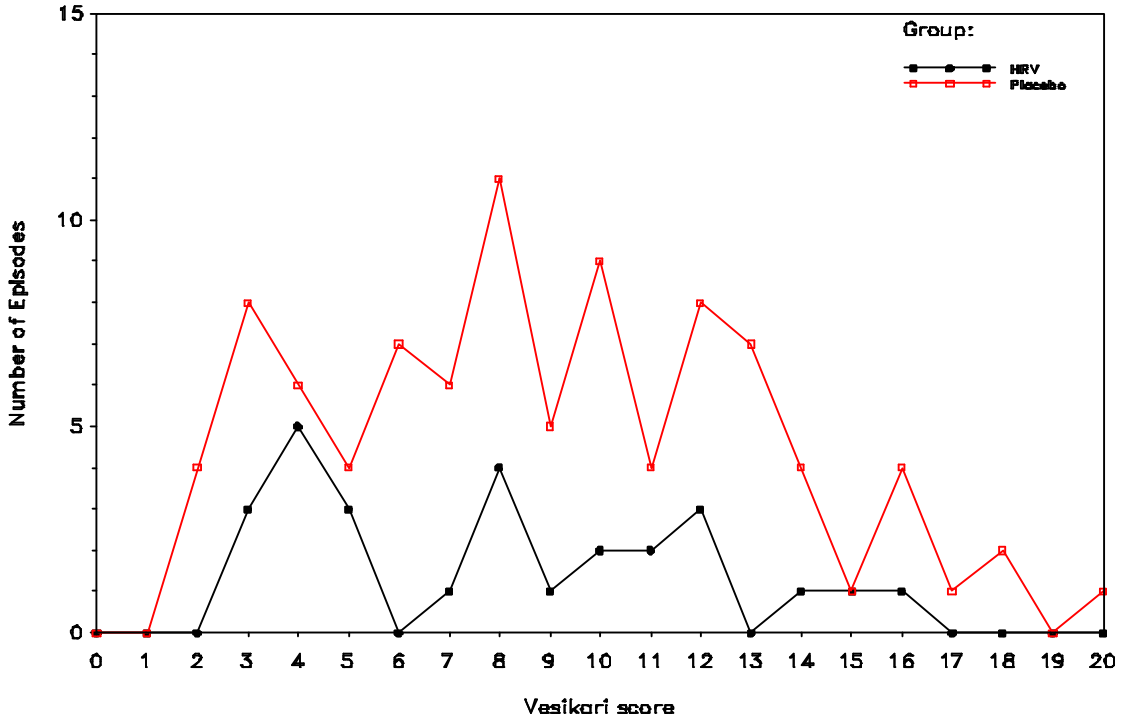
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 94 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 238 | 15.1 | 13.4 | 17.0 | 4.9 | -14.0 | 20.7 | 0.609 |
| Placebo | 1573 | 250 | 15.9 | 14.1 | 17.8 | - | - | - | - |

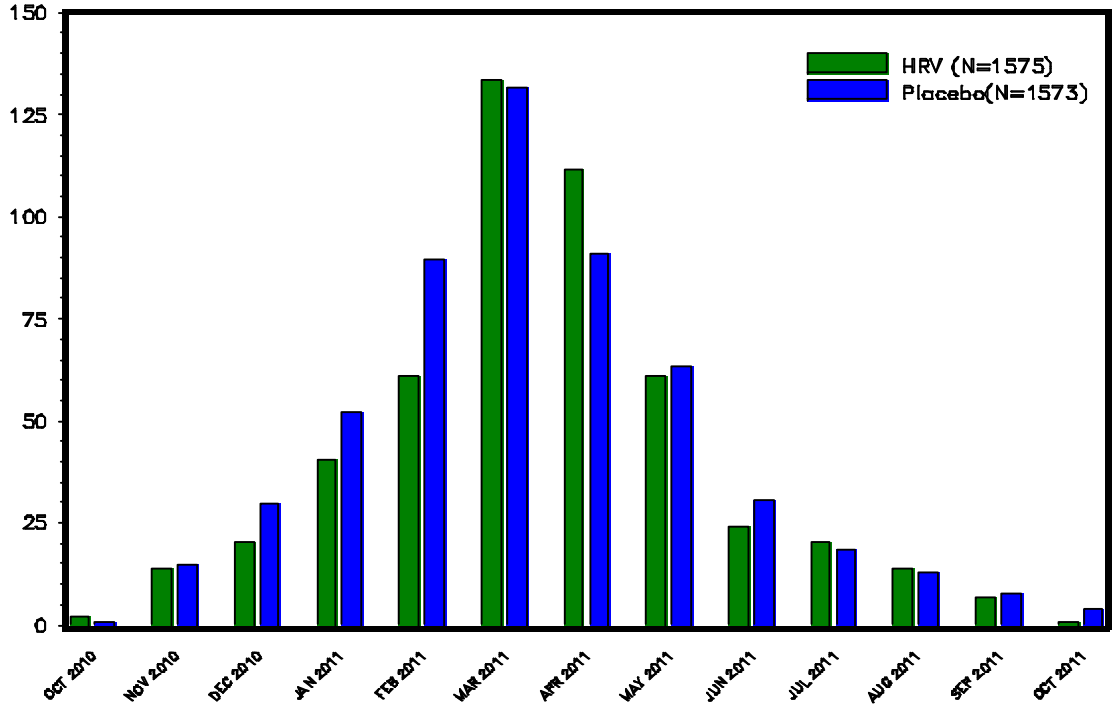
HRV = HRV
Placebo = Placebo
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 11 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after dose 2 up to Visit 6 (ATP cohort for efficacy)**



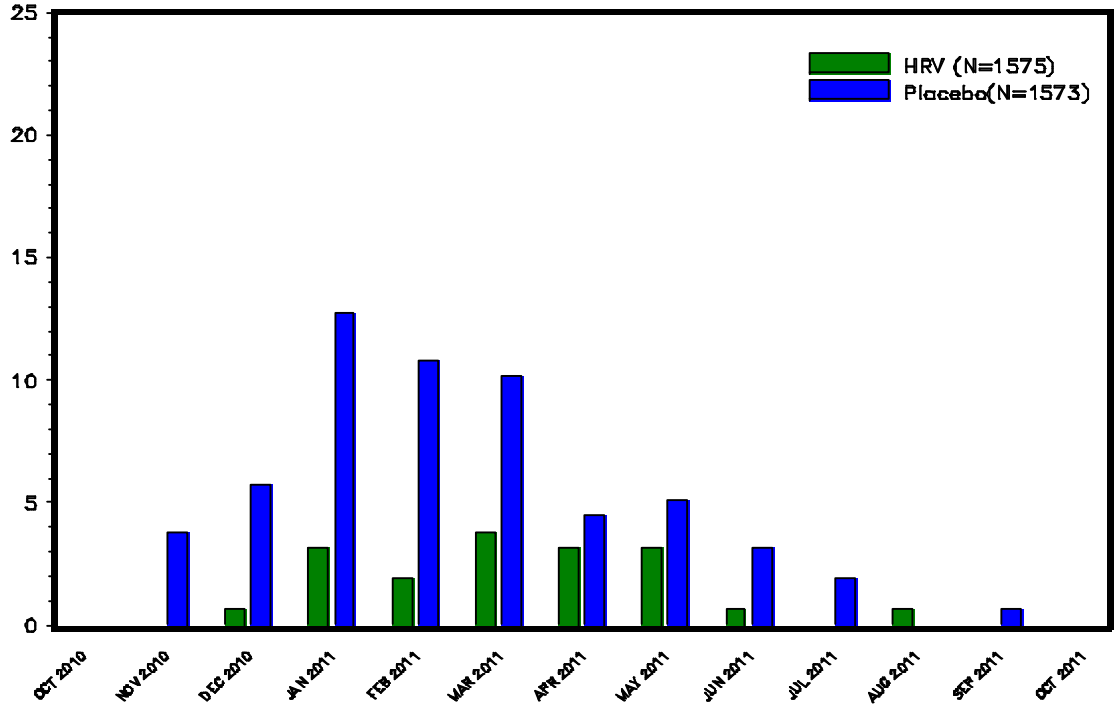

X axis = Score for each episodes computed based on the vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 12** **Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 6 for HRV group and placebo group (ATP cohort for efficacy)**



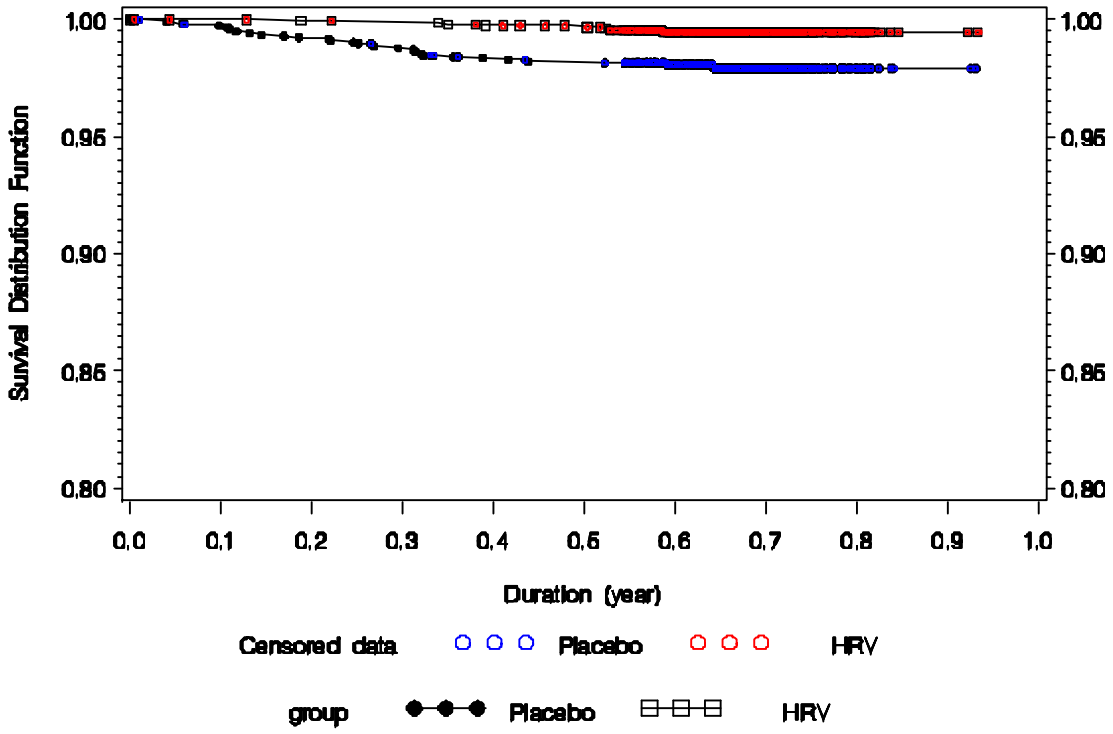

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 13** **Seasonal distribution of RVGE episodes reported from 2 weeks after Dose 2 up to Visit 6 for HRV group and placebo group (ATP cohort for efficacy)**



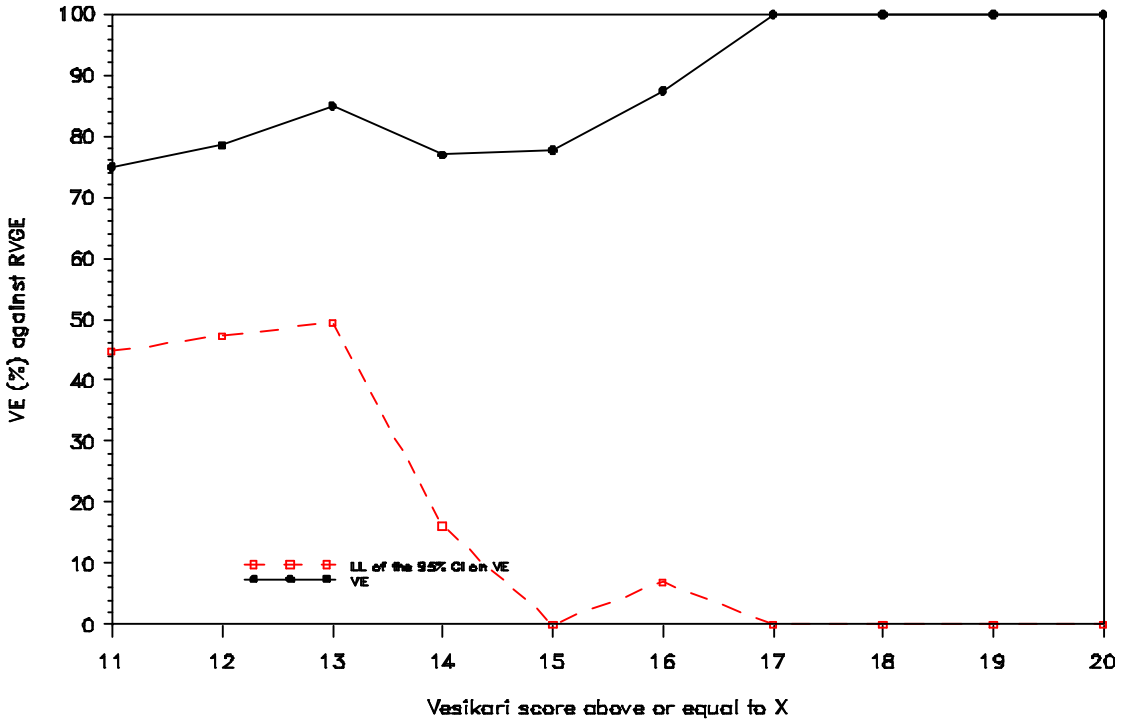

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 14 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



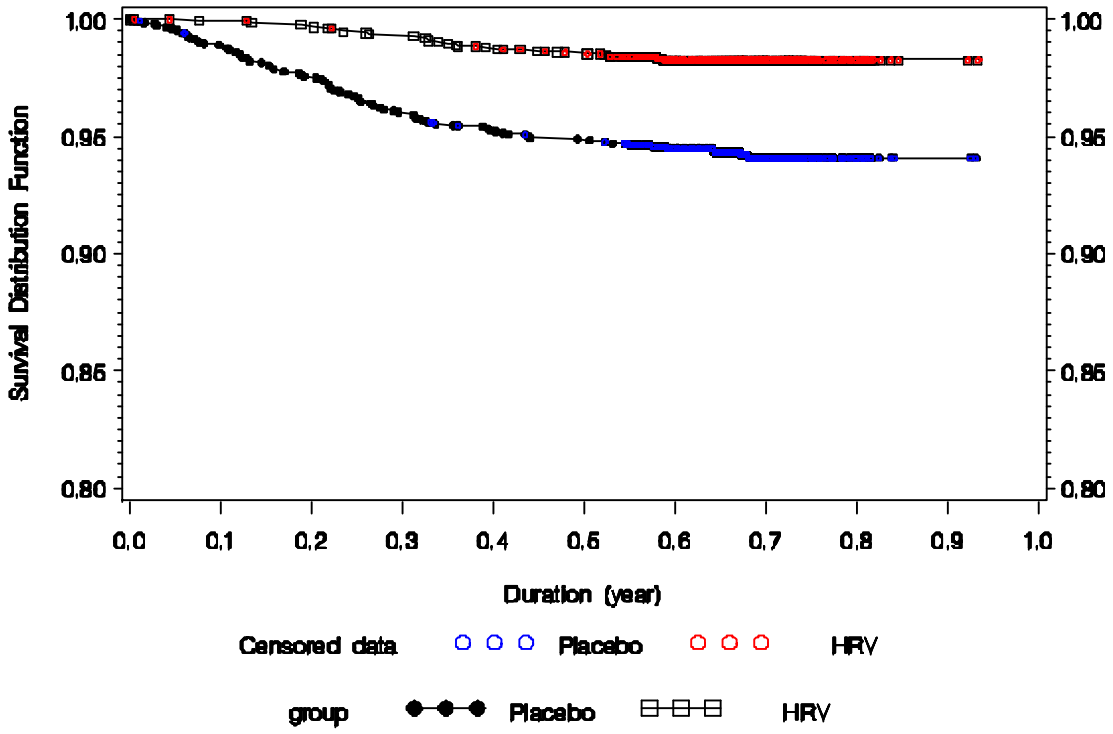

Y-axis has been cut at 0.8

**Figure 15 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from 2 weeks post dose 2 to visit 6 (ATP cohort for efficacy)**



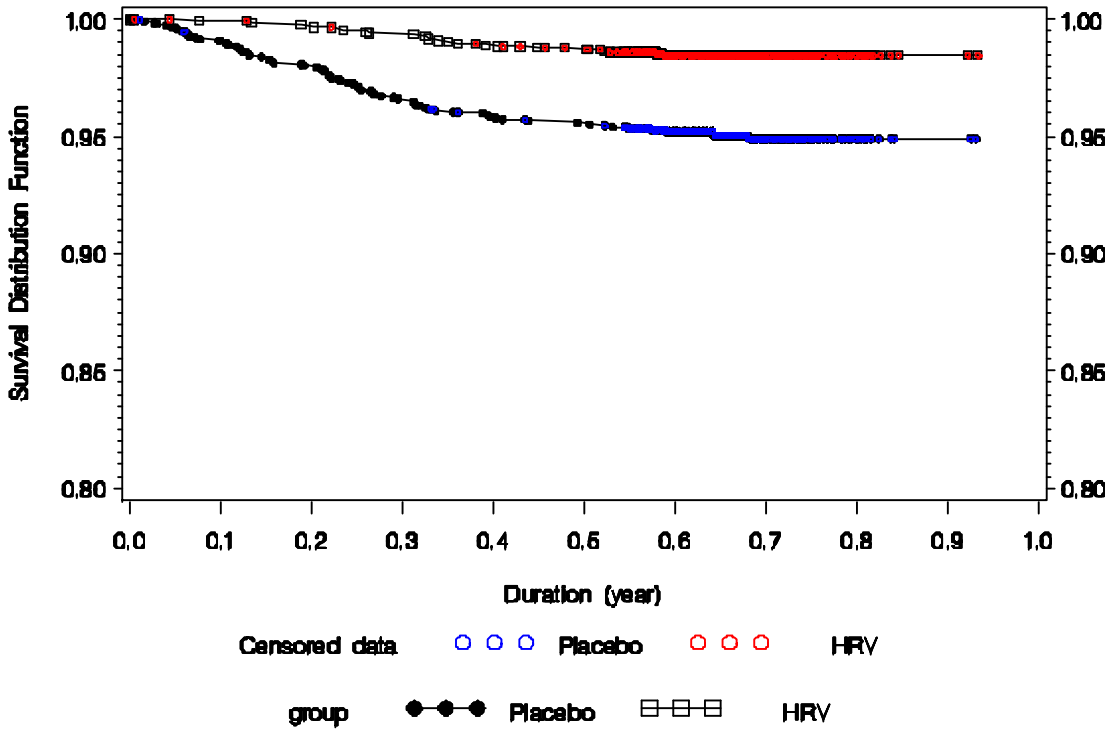

Y-axis has been cut at 0
X-axis is cut at 11
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 16** **The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



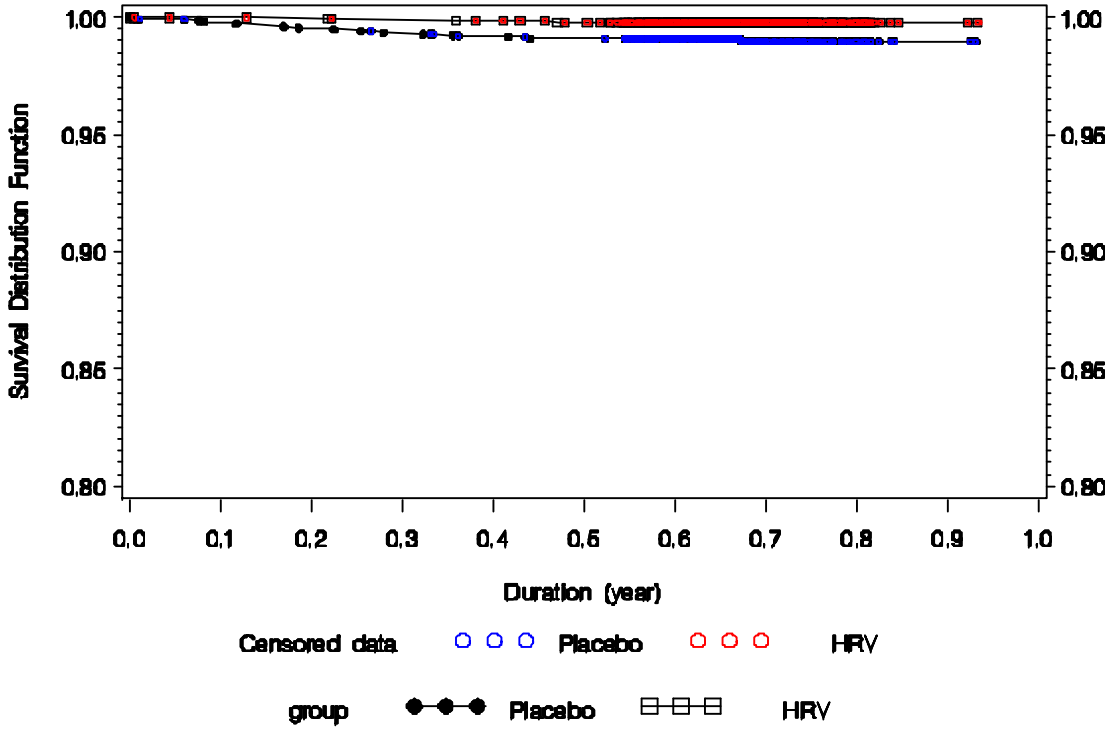

Y-axis has been cut at 0.8

**Figure 17 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



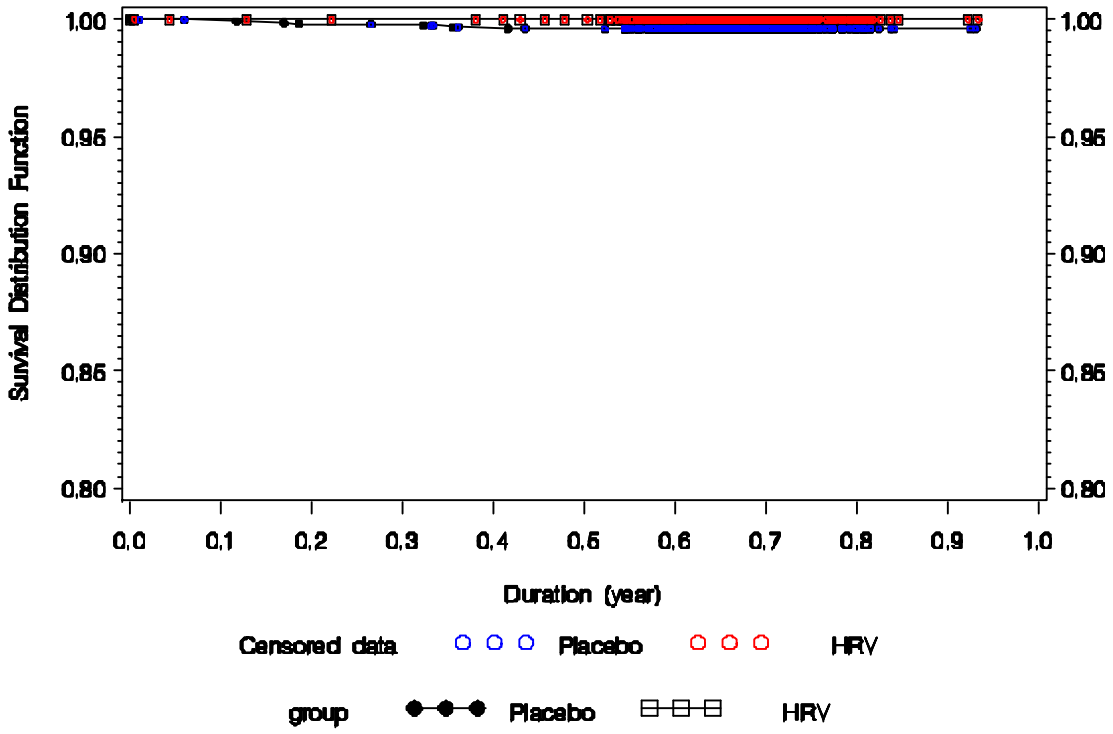

Y-axis has been cut at 0.8

**Figure 18 The Kaplan Meier curve for any RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



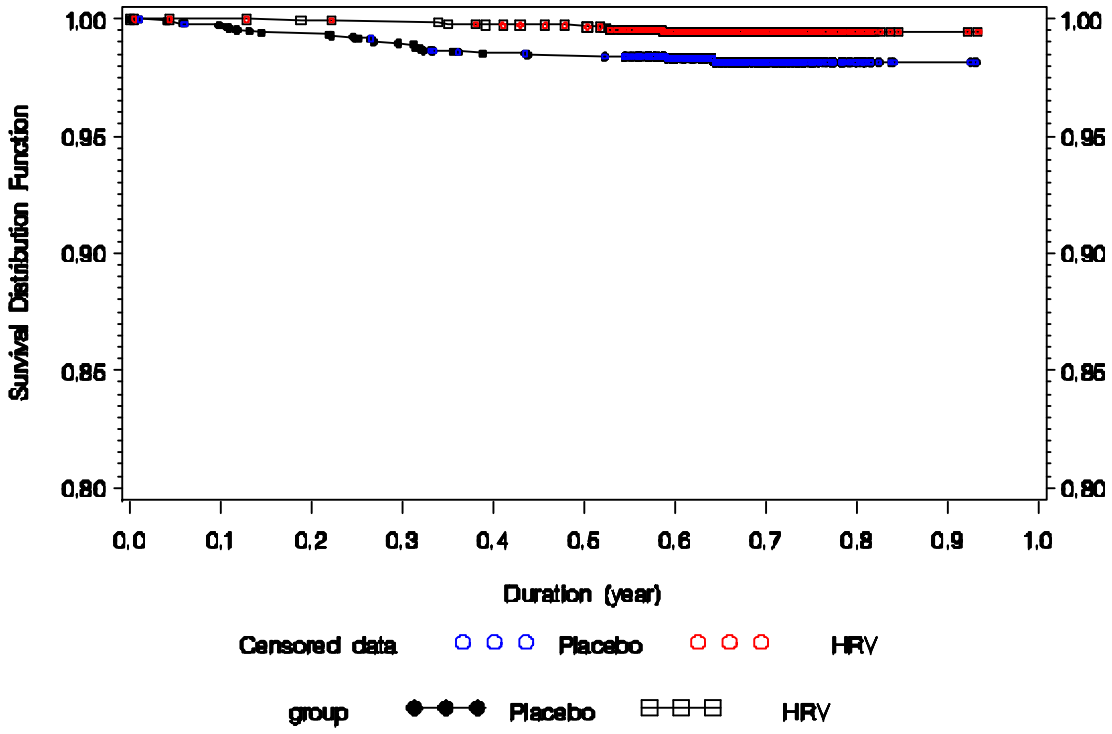

Y-axis has been cut at 0.8

**Figure 19 The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

**Figure 20** **The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

## 11.4.3. Characterization of GE episodes after Visit 6 up to Visit 7

### Table 95 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

| | | HRV N = 1500 | | Placebo N = 1479 | | Total N = 2979 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 1212 | 80.8 | 1171 | 79.2 | 2383 | 80.0 |
| | 1 | 242 | 16.1 | 252 | 17.0 | 494 | 16.6 |
| | 2 | 28 | 1.9 | 46 | 3.1 | 74 | 2.5 |
| | 3 | 13 | 0.9 | 6 | 0.4 | 19 | 0.6 |
| | 4 | 1 | 0.1 | 3 | 0.2 | 4 | 0.1 |
| | 5 | 2 | 0.1 | 1 | 0.1 | 3 | 0.1 |
| | 6 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | 8 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 288 | 19.2 | 308 | 20.8 | 596 | 20.0 |
| RVGE | 0 | 1457 | 97.1 | 1401 | 94.7 | 2858 | 95.9 |
| | 1 | 43 | 2.9 | 78 | 5.3 | 121 | 4.1 |
| | Any | 43 | 2.9 | 78 | 5.3 | 121 | 4.1 |
| Severe GE | 0 | 1428 | 95.2 | 1376 | 93.0 | 2804 | 94.1 |
| | 1 | 66 | 4.4 | 97 | 6.6 | 163 | 5.5 |
| | 2 | 3 | 0.2 | 4 | 0.3 | 7 | 0.2 |
| | 3 | 2 | 0.1 | 2 | 0.1 | 4 | 0.1 |
| | 4 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 72 | 4.8 | 103 | 7.0 | 175 | 5.9 |
| Severe RVGE | 0 | 1487 | 99.1 | 1436 | 97.1 | 2923 | 98.1 |
| | 1 | 13 | 0.9 | 43 | 2.9 | 56 | 1.9 |
| | Any | 13 | 0.9 | 43 | 2.9 | 56 | 1.9 |

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

### Table 96 Number of GE episodes reported from Visit 6 up to Visit 7 by severity using the 20-point Vesikari scale (ATP cohort for efficacy - second year follow-up period)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| **Event** | **Severity using 20 point Vesikari scale** | **n** | **%** | **n** | **%** |
| GE | Mild (1-6) | 163 | 44.7 | 155 | 40.9 |
| | Moderate (7-10) | 120 | 32.9 | 113 | 29.8 |
| | Severe (≥11) | 82 | 22.5 | 111 | 29.3 |
| | Any | 365 | 100 | 379 | 100 |
| RVGE | Mild (1-6) | 17 | 39.5 | 16 | 20.5 |
| | Moderate (7-10) | 13 | 30.2 | 19 | 24.4 |
| | Severe (≥11) | 13 | 30.2 | 43 | 55.1 |
| | Any | 43 | 100 | 78 | 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

## Table 97 Percentage of GE episodes with no available stool results from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

| | HRV N' = 365 | | Placebo N' = 379 | | Total N' = 744 | |
|---|---|---|---|---|---|---|
| **Categories** | **n** | **%** | **n** | **%** | **n** | **%** |
| No stool results available | 10 | 2.7 | 19 | 5.0 | 29 | 3.9 |
| no stools collected* | 8 | 2.2 | 18 | 4.7 | 26 | 3.5 |
| stools collected but no results available | 2 | 0.5 | 1 | 0.3 | 3 | 0.4 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category
*There is one episode of GE for which sample was collected but was not sent to lab. Hence the sample was not tested.

## Table 98 Percentage of subjects with RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

| | HRV N = 1500 | | Placebo N = 1479 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 43 | 2.9 | 78 | 5.3 |
| G1 WT | 19 | 1.3 | 31 | 2.1 |
| G2 | 20 | 1.3 | 37 | 2.5 |
| G3 | 1 | 0.1 | 4 | 0.3 |
| G9 | 1 | 0.1 | 4 | 0.3 |
| GX | 4 | 0.3 | 6 | 0.4 |
| P4 | 21 | 1.4 | 40 | 2.7 |
| P8 WT | 22 | 1.5 | 37 | 2.5 |
| P9 | 0 | 0.0 | 1 | 0.1 |
| PX | 1 | 0.1 | 0 | 0.0 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 99 Percentage of subjects with severe RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

| | HRV N = 1500 | | Placebo N = 1479 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 13 | 0.9 | 43 | 2.9 |
| G1 WT | 9 | 0.6 | 19 | 1.3 |
| G2 | 4 | 0.3 | 16 | 1.1 |
| G3 | 0 | 0.0 | 1 | 0.1 |
| G9 | 0 | 0.0 | 3 | 0.2 |
| GX | 0 | 0.0 | 6 | 0.4 |
| P4 | 5 | 0.3 | 18 | 1.2 |
| P8 WT | 8 | 0.5 | 24 | 1.6 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 100 Number of RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

| Serotype | HRV N'=43 | | Placebo N'=78 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 1.28 |
| G1WT+G2+P4+P8WT | 1 | 2.33 | 1 | 1.28 |
| G1WT+G2+P8WT | 0 | 0.00 | 2 | 2.56 |
| G1WT+P4 | 1 | 2.33 | 5 | 6.41 |
| G1WT+P8WT | 17 | 39.53 | 22 | 28.21 |
| G2+G3+P4 | 1 | 2.33 | 0 | 0.00 |
| G2+P4 | 18 | 41.86 | 33 | 42.31 |
| G3+P8WT | 0 | 0.00 | 3 | 3.85 |
| G3+P9 | 0 | 0.00 | 1 | 1.28 |
| G9+P8WT | 1 | 2.33 | 4 | 5.13 |
| GX | 0 | 0.00 | 1 | 1.28 |
| GX+P8WT | 3 | 6.98 | 5 | 6.41 |
| GX+PX | 1 | 2.33 | 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 Visit 6 up to Visit 7
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 101 Number of severe RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

| Serotype | HRV N'=13 | | Placebo N'=43 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 2.33 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 2.33 |
| G1WT+P4 | 1 | 7.69 | 3 | 6.98 |
| G1WT+P8WT | 8 | 61.54 | 14 | 32.56 |
| G2+P4 | 4 | 30.77 | 14 | 32.56 |
| G3+P8WT | 0 | 0.00 | 1 | 2.33 |
| G9+P8WT | 0 | 0.00 | 3 | 6.98 |
| GX | 0 | 0.00 | 1 | 2.33 |
| GX+P8WT | 0 | 0.00 | 5 | 11.63 |

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 severe RV GE episodes reported from Visit 6 up to Visit 7
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 102 Duration (in years) of efficacy follow-up period - from Visit 6 up to Visit 7 (ATP cohort for efficacy - second year follow-up period)

| | | HRV N = 1500 | Placebo N = 1479 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 1040 | 1029 |
| | Mean | 0.69 | 0.70 |
| | Minimum | 0.40 | 0.28 |
| | Q1 | 0.59 | 0.59 |
| | Median | 0.69 | 0.70 |
| | Q3 | 0.79 | 0.79 |
| | Maximum | 0.96 | 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

## 11.4.4. Vaccine efficacy from after Visit 6 up to Visit 7

### 11.4.4.1. Vaccine efficacy against severe RV GE

**Table 103 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 13 | 0.9 | 0.5 | 1.5 | 70.2 | 43.5 | 85.3 | <0.001 |
| Placebo | 1479 | 43 | 2.9 | 2.1 | 3.9 | - | - | - | - |

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

### 11.4.4.2. Vaccine efficacy against any RV GE

**Table 104 Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 43 | 2.9 | 2.1 | 3.8 | 45.6 | 20.1 | 63.4 | 0.001 |
| Placebo | 1479 | 78 | 5.3 | 4.2 | 6.5 | - | - | - | - |

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

### 11.4.4.3. Vaccine efficacy against circulating RV types

**Table 105 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1500 | 9 | 0.6 | 0.3 | 1.1 | 53.3 | -8.3 | 81.4 | 0.080 |
| | Placebo | 1479 | 19 | 1.3 | 0.8 | 2.0 | - | - | - | - |
| G2 | HRV | 1500 | 4 | 0.3 | 0.1 | 0.7 | 75.4 | 23.6 | 94.0 | 0.011 |
| | Placebo | 1479 | 16 | 1.1 | 0.6 | 1.8 | - | - | - | - |
| G3 | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3745.4 | 100.0 | 0.993 |
| | Placebo | 1479 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| G9 | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -138.6 | 100.0 | 0.245 |
| | Placebo | 1479 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| GX | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 16.3 | 100.0 | 0.030 |
| | Placebo | 1479 | 6 | 0.4 | 0.1 | 0.9 | - | - | - | - |
| P4 | HRV | 1500 | 5 | 0.3 | 0.1 | 0.8 | 72.6 | 23.5 | 92.1 | 0.010 |
| | Placebo | 1479 | 18 | 1.2 | 0.7 | 1.9 | - | - | - | - |
| P8 WT | HRV | 1500 | 8 | 0.5 | 0.2 | 1.0 | 67.1 | 24.4 | 87.2 | 0.006 |
| | Placebo | 1479 | 24 | 1.6 | 1.0 | 2.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1500 | 4 | 0.3 | 0.1 | 0.7 | 84.8 | 56.3 | 96.2 | <0.001 |
| | Placebo | 1479 | 26 | 1.8 | 1.2 | 2.6 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 106 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1500 | 19 | 1.3 | 0.8 | 2.0 | 39.6 | -10.4 | 67.7 | 0.108 |
| | Placebo | 1479 | 31 | 2.1 | 1.4 | 3.0 | - | - | - | - |
| G2 | HRV | 1500 | 20 | 1.3 | 0.8 | 2.1 | 46.7 | 5.8 | 70.7 | 0.029 |
| | Placebo | 1479 | 37 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| G3 | HRV | 1500 | 1 | 0.1 | 0.0 | 0.4 | 75.4 | -149.1 | 99.5 | 0.366 |
| | Placebo | 1479 | 4 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G9 | HRV | 1500 | 1 | 0.1 | 0.0 | 0.4 | 75.4 | -149.1 | 99.5 | 0.366 |
| | Placebo | 1479 | 4 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| GX | HRV | 1500 | 4 | 0.3 | 0.1 | 0.7 | 34.3 | -177.2 | 86.4 | 0.737 |
| | Placebo | 1479 | 6 | 0.4 | 0.1 | 0.9 | - | - | - | - |
| P4 | HRV | 1500 | 21 | 1.4 | 0.9 | 2.1 | 48.2 | 10.1 | 71.0 | 0.018 |
| | Placebo | 1479 | 40 | 2.7 | 1.9 | 3.7 | - | - | - | - |
| P8 WT | HRV | 1500 | 22 | 1.5 | 0.9 | 2.2 | 41.4 | -2.0 | 67.1 | 0.060 |
| | Placebo | 1479 | 37 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| P9 | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3745.4 | 100.0 | 0.993 |
| | Placebo | 1479 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| PX | HRV | 1500 | 1 | 0.1 | 0.0 | 0.4 | Und. | Und. | Und. | 1.000 |
| | Placebo | 1479 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1500 | 25 | 1.7 | 1.1 | 2.5 | 51.7 | 20.5 | 71.3 | 0.003 |
| | Placebo | 1479 | 51 | 3.4 | 2.6 | 4.5 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain
Und. = cannot be estimated

### 11.4.4.4. Vaccine efficacy against hospitalisation due to RV

**Table 107 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 2 | 0.1 | 0.0 | 0.5 | 71.8 | -48.0 | 97.1 | 0.173 |
| Placebo | 1479 | 7 | 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
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

### 11.4.4.5. Vaccine efficacy against all cause GE

**Table 108 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 288 | 19.2 | 17.2 | 21.3 | 7.8 | -8.6 | 21.8 | 0.342 |
| Placebo | 1479 | 308 | 20.8 | 18.8 | 23.0 | - | - | - | - |

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

**Table 109 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 72 | 4.8 | 3.8 | 6.0 | 31.1 | 6.0 | 49.7 | 0.018 |
| Placebo | 1479 | 103 | 7.0 | 5.7 | 8.4 | - | - | - | - |

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

**Table 110 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 6 | 0.4 | 0.1 | 0.9 | 78.9 | 48.0 | 92.8 | <0.001 |
| Placebo | 1479 | 28 | 1.9 | 1.3 | 2.7 | - | - | - | - |

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

# 11.5. Total vaccinated cohort analysis

## 11.5.1. Characterization of GE episodes from Dose 1 to Visit 7

### Table 111 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 up to Visit 7 (Total vaccinated cohort)

| Group | N | n | % | 95%CI | |
|---|---|---|---|---|---|
| | | | | LL | UL |
| **HRV** | 1666 | 2 | 0.1 | 0.0 | 0.4 |
| **Placebo** | 1667 | 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

### Table 112 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 817 | 49.0 | 800 | 48.0 | 1617 | 48.5 |
| | 1 | 508 | 30.5 | 496 | 29.8 | 1004 | 30.1 |
| | 2 | 205 | 12.3 | 229 | 13.7 | 434 | 13.0 |
| | 3 | 83 | 5.0 | 79 | 4.7 | 162 | 4.9 |
| | 4 | 25 | 1.5 | 35 | 2.1 | 60 | 1.8 |
| | 5 | 14 | 0.8 | 12 | 0.7 | 26 | 0.8 |
| | 6 | 9 | 0.5 | 8 | 0.5 | 17 | 0.5 |
| | 7 | 2 | 0.1 | 3 | 0.2 | 5 | 0.2 |
| | 8 | 0 | 0.0 | 2 | 0.1 | 2 | 0.1 |
| | 9 | 3 | 0.2 | 1 | 0.1 | 4 | 0.1 |
| | 10 | 0 | 0.0 | 2 | 0.1 | 2 | 0.1 |
| | Any | 849 | 51.0 | 867 | 52.0 | 1716 | 51.5 |
| RVGE | 0 | 1591 | 95.5 | 1491 | 89.4 | 3082 | 92.5 |
| | 1 | 75 | 4.5 | 172 | 10.3 | 247 | 7.4 |
| | 2 | 0 | 0.0 | 4 | 0.2 | 4 | 0.1 |
| | Any | 75 | 4.5 | 176 | 10.6 | 251 | 7.5 |
| Severe GE | 0 | 1456 | 87.4 | 1427 | 85.6 | 2883 | 86.5 |
| | 1 | 192 | 11.5 | 203 | 12.2 | 395 | 11.9 |
| | 2 | 10 | 0.6 | 31 | 1.9 | 41 | 1.2 |
| | 3 | 5 | 0.3 | 6 | 0.4 | 11 | 0.3 |
| | 4 | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| | 5 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 210 | 12.6 | 240 | 14.4 | 450 | 13.5 |
| Severe RVGE | 0 | 1641 | 98.5 | 1591 | 95.4 | 3232 | 97.0 |
| | 1 | 25 | 1.5 | 76 | 4.6 | 101 | 3.0 |
| | Any | 25 | 1.5 | 76 | 4.6 | 101 | 3.0 |

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

## Table 113 Number of GE episodes reported from Dose 1 up to Visit 7 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 778 | 54.3 | 812 | 54.0 |
| | Moderate (7-10) | 405 | 28.3 | 403 | 26.8 |
| | Severe (≥11) | 240 | 16.8 | 283 | 18.8 |
| | Unknown | 9 | 0.6 | 7 | 0.5 |
| | Any | 1423 | 99.4 | 1498 | 99.5 |
| RVGE | Mild (1-6) | 29 | 38.7 | 49 | 27.2 |
| | Moderate (7-10) | 21 | 28.0 | 55 | 30.6 |
| | Severe (≥11) | 25 | 33.3 | 76 | 42.2 |
| | Any | 75 | 100 | 180 | 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

## Table 114 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | HRV N' = 1432 | | Placebo N' = 1505 | | Total N' = 2937 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 171 | 11.9 | 165 | 11.0 | 336 | 11.4 |
| no stools collected* | 169 | 11.8 | 164 | 10.9 | 333 | 11.3 |
| stools collected but no results available | 2 | 0.1 | 1 | 0.1 | 3 | 0.1 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category
*There is one episode of GE for which sample was collected but was not sent to lab. Hence the sample was not tested.

## Table 115 Percentage of subjects with RV GE episodes from Dose 1 up to Visit 7 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| Serotype | n | % | n | % |
| Any | 75 | 4.5 | 176 | 10.6 |
| G1 WT | 22 | 1.3 | 51 | 3.1 |
| G2 | 46 | 2.8 | 110 | 6.6 |
| G3 | 2 | 0.1 | 12 | 0.7 |
| G9 | 1 | 0.1 | 5 | 0.3 |
| GX | 6 | 0.4 | 8 | 0.5 |
| P4 | 47 | 2.8 | 113 | 6.8 |
| P8 WT | 26 | 1.6 | 63 | 3.8 |
| P9 | 0 | 0.0 | 1 | 0.1 |
| PX | 4 | 0.2 | 1 | 0.1 |

WT=Wild Type
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=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 116 Percentage of subjects with severe RV GE episodes from Dose 1 up to Visit 7 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 25 | 1.5 | 76 | 4.6 |
| G1 WT | 9 | 0.5 | 25 | 1.5 |
| G2 | 14 | 0.8 | 44 | 2.6 |
| G3 | 1 | 0.1 | 3 | 0.2 |
| G9 | 0 | 0.0 | 3 | 0.2 |
| GX | 1 | 0.1 | 6 | 0.4 |
| P4 | 15 | 0.9 | 44 | 2.6 |
| P8 WT | 10 | 0.6 | 31 | 1.9 |
| PX | 1 | 0.1 | 1 | 0.1 |

WT=Wild Type
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=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 117 Number of RV GE episodes reported from Dose 1 up to Visit 7, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=75 | | Placebo N'=180 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+G2+P4 | 0 | 0.00 | 4 | 2.22 |
| G1WT+G2+P4+P8WT | 1 | 1.33 | 1 | 0.56 |
| G1WT+G2+P8WT | 0 | 0.00 | 3 | 1.67 |
| G1WT+P4 | 1 | 1.33 | 6 | 3.33 |
| G1WT+P8WT | 19 | 25.33 | 38 | 21.11 |
| G1WT+PX | 1 | 1.33 | 0 | 0.00 |
| G2+G3+P4 | 1 | 1.33 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 0.56 |
| G2+P4 | 43 | 57.33 | 102 | 56.67 |
| G2+P4+P8WT | 1 | 1.33 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 0.56 |
| G3+P8WT | 1 | 1.33 | 10 | 5.56 |
| G3+P9 | 0 | 0.00 | 1 | 0.56 |
| G9+P8WT | 1 | 1.33 | 5 | 2.78 |
| GX | 0 | 0.00 | 2 | 1.11 |
| GX+P8WT | 3 | 4.00 | 6 | 3.33 |
| GX+PX | 3 | 4.00 | 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 7
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 118 Number of severe RV GE episodes reported from Dose 1 up to Visit 7, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=25 | | Placebo N,=76 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 2 | 2.63 |
| G1WT+G2+P8WT | 0 | 0.00 | 2 | 2.63 |
| G1WT+P4 | 1 | 4.00 | 3 | 3.95 |
| G1WT+P8WT | 8 | 32.00 | 18 | 23.68 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.32 |
| G2+P4 | 13 | 52.00 | 38 | 50.00 |
| G2+P4+P8WT | 1 | 4.00 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.32 |
| G3+P8WT | 1 | 4.00 | 2 | 2.63 |
| G9+P8WT | 0 | 0.00 | 3 | 3.95 |
| GX | 0 | 0.00 | 1 | 1.32 |
| GX+P8WT | 0 | 0.00 | 5 | 6.58 |
| GX+PX | 1 | 4.00 | 0 | 0.00 |

WT=Wild Type
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 severe RV GE episodes reported from dose 1 of HRV vaccine or placebo up to visit 7
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 119 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | HRV N' = 75 | | Placebo N' = 180 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.2 | - | 9.9 | - |
| | SD | 3.8 | - | 4.6 | - |
| | Median | 8.0 | - | 10.0 | - |
| | Minimum | 2.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 63 | 84.0 | 109 | 60.6 |
| | 5 | 7 | 9.3 | 29 | 16.1 |
| | more than 5 days | 5 | 6.7 | 42 | 23.3 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 7 | 9.3 | 20 | 11.1 |
| | 4 to 5 | 38 | 50.7 | 77 | 42.8 |
| | more than 5 | 30 | 40.0 | 83 | 46.1 |
| Duration of vomiting (days) | 0 day | 40 | 53.3 | 68 | 37.8 |
| | 1 day | 13 | 17.3 | 47 | 26.1 |
| | 2 days | 17 | 22.7 | 31 | 17.2 |
| | more than 2 days | 5 | 6.7 | 34 | 18.9 |
| Max number of episodes of vomiting /day | 0 | 40 | 53.3 | 68 | 37.8 |
| | 1 | 8 | 10.7 | 28 | 15.6 |
| | 2 to 4 | 23 | 30.7 | 66 | 36.7 |
| | more than 4 | 4 | 5.3 | 18 | 10.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 17 | 22.7 | 45 | 25.0 |
| | 36.6 to 37.9°C | 35 | 46.7 | 78 | 43.3 |
| | 38.0 to 38.4°C | 14 | 18.7 | 18 | 10.0 |
| | more than 38.4°C | 9 | 12.0 | 39 | 21.7 |
| Treatment | none | 39 | 52.0 | 79 | 43.9 |
| | rehydration | 32 | 42.7 | 80 | 44.4 |
| | hospitalization | 4 | 5.3 | 21 | 11.7 |
| Dehydration | none | 39 | 52.0 | 79 | 43.9 |
| | 1 to 5% | 16 | 21.3 | 19 | 10.6 |
| | more than 5 % | 20 | 26.7 | 82 | 45.6 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 120 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G1WT type (Total vaccinated cohort)

| | | HRV N' = 22 | | Placebo N' = 52 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.8 | - | 10.8 | - |
| | SD | 4.0 | - | 4.4 | - |
| | Median | 9.5 | - | 10.0 | - |
| | Minimum | 2.0 | - | 3.0 | - |
| | Maximum | 16.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 21 | 95.5 | 28 | 53.8 |
| | 5 | 1 | 4.5 | 11 | 21.2 |
| | more than 5 days | 0 | 0.0 | 13 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 2 | 9.1 | 1 | 1.9 |
| | 4 to 5 | 9 | 40.9 | 30 | 57.7 |
| | more than 5 | 11 | 50.0 | 21 | 40.4 |
| Duration of vomiting (days) | 0 day | 12 | 54.5 | 15 | 28.8 |
| | 1 day | 2 | 9.1 | 15 | 28.8 |
| | 2 days | 6 | 27.3 | 11 | 21.2 |
| | more than 2 days | 2 | 9.1 | 11 | 21.2 |
| Max number of episodes of vomiting /day | 0 | 12 | 54.5 | 15 | 28.8 |
| | 1 | 2 | 9.1 | 9 | 17.3 |
| | 2 to 4 | 7 | 31.8 | 21 | 40.4 |
| | more than 4 | 1 | 4.5 | 7 | 13.5 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 3 | 13.6 | 12 | 23.1 |
| | 36.6 to 37.9°C | 8 | 36.4 | 22 | 42.3 |
| | 38.0 to 38.4°C | 7 | 31.8 | 6 | 11.5 |
| | more than 38.4°C | 4 | 18.2 | 12 | 23.1 |
| Treatment | none | 10 | 45.5 | 18 | 34.6 |
| | rehydration | 11 | 50.0 | 26 | 50.0 |
| | hospitalization | 1 | 4.5 | 8 | 15.4 |
| Dehydration | none | 10 | 45.5 | 18 | 34.6 |
| | 1 to 5% | 5 | 22.7 | 5 | 9.6 |
| | more than 5 % | 7 | 31.8 | 29 | 55.8 |

WT = Wild Type
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 121 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G2 type (Total vaccinated cohort)

| | | HRV N' = 46 | | Placebo N' = 112 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.1 | - | 9.4 | - |
| | SD | 3.8 | - | 4.6 | - |
| | Median | 8.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 38 | 82.6 | 70 | 62.5 |
| | 5 | 4 | 8.7 | 15 | 13.4 |
| | more than 5 days | 4 | 8.7 | 27 | 24.1 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 5 | 10.9 | 17 | 15.2 |
| | 4 to 5 | 24 | 52.2 | 42 | 37.5 |
| | more than 5 | 17 | 37.0 | 53 | 47.3 |
| Duration of vomiting (days) | 0 day | 24 | 52.2 | 45 | 40.2 |
| | 1 day | 10 | 21.7 | 31 | 27.7 |
| | 2 days | 9 | 19.6 | 18 | 16.1 |
| | more than 2 days | 3 | 6.5 | 18 | 16.1 |
| Max number of episodes of vomiting /day | 0 | 24 | 52.2 | 45 | 40.2 |
| | 1 | 5 | 10.9 | 15 | 13.4 |
| | 2 to 4 | 15 | 32.6 | 41 | 36.6 |
| | more than 4 | 2 | 4.3 | 11 | 9.8 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 13 | 28.3 | 30 | 26.8 |
| | 36.6 to 37.9°C | 21 | 45.7 | 47 | 42.0 |
| | 38.0 to 38.4°C | 8 | 17.4 | 12 | 10.7 |
| | more than 38.4°C | 4 | 8.7 | 23 | 20.5 |
| Treatment | none | 24 | 52.2 | 57 | 50.9 |
| | rehydration | 19 | 41.3 | 42 | 37.5 |
| | hospitalization | 3 | 6.5 | 13 | 11.6 |
| Dehydration | none | 24 | 52.2 | 57 | 50.9 |
| | 1 to 5% | 9 | 19.6 | 12 | 10.7 |
| | more than 5 % | 13 | 28.3 | 43 | 38.4 |

N' = number of RV GE episodes reported in each group
n/% = number/percentage of specified symptom reported in each group among N'
Value= value of the considered parameter
SD= standard deviation
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 122 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G3 type (Total vaccinated cohort)

| | | HRV N' = 2 | | Placebo N' = 12 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.5 | - | 8.8 | - |
| | SD | 4.9 | - | 4.3 | - |
| | Median | 7.5 | - | 8.5 | - |
| | Minimum | 4.0 | - | 2.0 | - |
| | Maximum | 11.0 | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 2 | 100 | 8 | 66.7 |
| | 5 | 0 | 0.0 | 1 | 8.3 |
| | more than 5 days | 0 | 0.0 | 3 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 50.0 | 2 | 16.7 |
| | 4 to 5 | 0 | 0.0 | 6 | 50.0 |
| | more than 5 | 1 | 50.0 | 4 | 33.3 |
| Duration of vomiting (days) | 0 day | 0 | 0.0 | 5 | 41.7 |
| | 1 day | 1 | 50.0 | 2 | 16.7 |
| | 2 days | 1 | 50.0 | 4 | 33.3 |
| | more than 2 days | 0 | 0.0 | 1 | 8.3 |
| Max number of episodes of vomiting /day | 0 | 0 | 0.0 | 5 | 41.7 |
| | 1 | 1 | 50.0 | 4 | 33.3 |
| | 2 to 4 | 1 | 50.0 | 2 | 16.7 |
| | more than 4 | 0 | 0.0 | 1 | 8.3 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 50.0 | 4 | 33.3 |
| | 36.6 to 37.9°C | 0 | 0.0 | 5 | 41.7 |
| | 38.0 to 38.4°C | 0 | 0.0 | 1 | 8.3 |
| | more than 38.4°C | 1 | 50.0 | 2 | 16.7 |
| Treatment | none | 2 | 100 | 6 | 50.0 |
| | rehydration | 0 | 0.0 | 6 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 2 | 100 | 6 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 8.3 |
| | more than 5 % | 0 | 0.0 | 5 | 41.7 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 123 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G9 type (Total vaccinated cohort)

| | | HRV N' = 1 | | Placebo N' = 5 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 4.0 | - | 10.6 | - |
| | SD | 0.0 | - | 4.0 | - |
| | Median | 4.0 | - | 12.0 | - |
| | Minimum | 4.0 | - | 5.0 | - |
| | Maximum | 4.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 3 | 60.0 |
| | 5 | 0 | 0.0 | 1 | 20.0 |
| | more than 5 days | 0 | 0.0 | 1 | 20.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 0 | 0.0 |
| | 4 to 5 | 1 | 100 | 3 | 60.0 |
| | more than 5 | 0 | 0.0 | 2 | 40.0 |
| Duration of vomiting (days) | 0 day | 1 | 100 | 2 | 40.0 |
| | 1 day | 0 | 0.0 | 1 | 20.0 |
| | 2 days | 0 | 0.0 | 2 | 40.0 |
| | more than 2 days | 0 | 0.0 | 0 | 0.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 100 | 2 | 40.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |
| | 2 to 4 | 0 | 0.0 | 3 | 60.0 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 0 | 0.0 |
| | 36.6 to 37.9°C | 1 | 100 | 4 | 80.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 1 | 20.0 |
| Treatment | none | 1 | 100 | 1 | 20.0 |
| | rehydration | 0 | 0.0 | 4 | 80.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 1 | 20.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 20.0 |
| | more than 5 % | 0 | 0.0 | 3 | 60.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 124 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By GX type (Total vaccinated cohort)

| | | HRV N' = 6 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.7 | - | 13.4 | - |
| | SD | 2.6 | - | 3.5 | - |
| | Median | 7.0 | - | 14.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 50.0 | 5 | 62.5 |
| | 5 | 2 | 33.3 | 2 | 25.0 |
| | more than 5 days | 1 | 16.7 | 1 | 12.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 12.5 |
| | 4 to 5 | 4 | 66.7 | 1 | 12.5 |
| | more than 5 | 2 | 33.3 | 6 | 75.0 |
| Duration of vomiting (days) | 0 day | 4 | 66.7 | 1 | 12.5 |
| | 1 day | 1 | 16.7 | 2 | 25.0 |
| | 2 days | 1 | 16.7 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 5 | 62.5 |
| Max number of episodes of vomiting /day | 0 | 4 | 66.7 | 1 | 12.5 |
| | 1 | 1 | 16.7 | 1 | 12.5 |
| | 2 to 4 | 0 | 0.0 | 4 | 50.0 |
| | more than 4 | 1 | 16.7 | 2 | 25.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 16.7 | 1 | 12.5 |
| | 36.6 to 37.9°C | 5 | 83.3 | 4 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 3 | 37.5 |
| Treatment | none | 3 | 50.0 | 1 | 12.5 |
| | rehydration | 3 | 50.0 | 6 | 75.0 |
| | hospitalization | 0 | 0.0 | 1 | 12.5 |
| Dehydration | none | 3 | 50.0 | 1 | 12.5 |
| | 1 to 5% | 2 | 33.3 | 0 | 0.0 |
| | more than 5 % | 1 | 16.7 | 7 | 87.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain

## Table 125 Characteristics of the GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | HRV N' = 1432 | | Placebo N' = 1505 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.6 | - | 7.0 | - |
| | SD | 3.7 | - | 4.0 | - |
| | Median | 6.0 | - | 6.0 | - |
| | Minimum | 0.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 15 | 1.0 | 12 | 0.8 |
| | 1 to 4 days | 1022 | 71.4 | 1024 | 68.0 |
| | 5 | 145 | 10.1 | 163 | 10.8 |
| | more than 5 days | 250 | 17.5 | 306 | 20.3 |
| Maximum number of looser than normal stools/day | 0 | 15 | 1.0 | 12 | 0.8 |
| | 1 to 3 | 255 | 17.8 | 255 | 16.9 |
| | 4 to 5 | 721 | 50.3 | 761 | 50.6 |
| | more than 5 | 441 | 30.8 | 477 | 31.7 |
| Duration of vomiting (days) | 0 day | 1021 | 71.3 | 1039 | 69.0 |
| | 1 day | 205 | 14.3 | 227 | 15.1 |
| | 2 days | 113 | 7.9 | 108 | 7.2 |
| | more than 2 days | 93 | 6.5 | 131 | 8.7 |
| Max number of episodes of vomiting /day | 0 | 1021 | 71.3 | 1039 | 69.0 |
| | 1 | 132 | 9.2 | 161 | 10.7 |
| | 2 to 4 | 241 | 16.8 | 242 | 16.1 |
| | more than 4 | 38 | 2.7 | 63 | 4.2 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 584 | 40.8 | 603 | 40.1 |
| | 36.6 to 37.9°C | 652 | 45.5 | 679 | 45.1 |
| | 38.0 to 38.4°C | 78 | 5.4 | 88 | 5.8 |
| | more than 38.4°C | 118 | 8.2 | 135 | 9.0 |
| Treatment | none | 934 | 65.2 | 962 | 63.9 |
| | rehydration | 444 | 31.0 | 444 | 29.5 |
| | hospitalization | 54 | 3.8 | 99 | 6.6 |
| Dehydration | none | 934 | 65.2 | 962 | 63.9 |
| | 1 to 5% | 208 | 14.5 | 190 | 12.6 |
| | more than 5 % | 290 | 20.3 | 353 | 23.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 126 Duration (in years) of efficacy follow-up period - from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 2351 | 2334 |
| | Mean | 1.41 | 1.40 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 1.39 | 1.38 |
| | Median | 1.50 | 1.50 |
| | Q3 | 1.59 | 1.58 |
| | Maximum | 1.68 | 1.68 |

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

## 11.5.2. Vaccine efficacy during the period from Dose 1 up to Visit 7

### 11.5.2.1. Vaccine efficacy against severe RV GE

**Table 127 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1666 | 25 | 1.5 | 1.0 | 2.2 | 67.1 | 47.7 | 79.9 | <0.001 |
| Placebo | 1667 | 76 | 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
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 128 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Severity using Vesikari scale** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| ≥11 | HRV | 1666 | 25 | 1.5 | 1.0 | 2.2 | 67.1 | 47.7 | 79.9 | <0.001 |
| | Placebo | 1667 | 76 | 4.6 | 3.6 | 5.7 | - | - | - | - |
| ≥12 | HRV | 1666 | 18 | 1.1 | 0.6 | 1.7 | 73.9 | 55.6 | 85.4 | <0.001 |
| | Placebo | 1667 | 69 | 4.1 | 3.2 | 5.2 | - | - | - | - |
| ≥13 | HRV | 1666 | 9 | 0.5 | 0.2 | 1.0 | 84.2 | 67.9 | 93.1 | <0.001 |
| | Placebo | 1667 | 57 | 3.4 | 2.6 | 4.4 | - | - | - | - |
| ≥14 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 83.0 | 63.6 | 93.0 | <0.001 |
| | Placebo | 1667 | 47 | 2.8 | 2.1 | 3.7 | - | - | - | - |
| ≥15 | HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | 89.2 | 69.9 | 97.2 | <0.001 |
| | Placebo | 1667 | 37 | 2.2 | 1.6 | 3.0 | - | - | - | - |
| ≥16 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 92.6 | 70.5 | 99.1 | <0.001 |
| | Placebo | 1667 | 27 | 1.6 | 1.1 | 2.3 | - | - | - | - |
| ≥17 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 67.2 | 100.0 | <0.001 |
| | Placebo | 1667 | 13 | 0.8 | 0.4 | 1.3 | - | - | - | - |
| ≥18 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 49.3 | 100.0 | 0.004 |
| | Placebo | 1667 | 9 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| ≥19 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -432.8 | 100.0 | 0.500 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| =20 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 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 a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.5.2.2. Vaccine efficacy against any RV GE

**Table 129 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1666 | 75 | 4.5 | 3.6 | 5.6 | 57.4 | 43.8 | 67.9 | <0.001 |
| Placebo | 1667 | 176 | 10.6 | 9.1 | 12.1 | - | - | - | - |

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

### 11.5.2.3. Vaccine efficacy against circulating RV types

**Table 130 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by RV type (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1666 | 9 | 0.5 | 0.2 | 1.0 | 64.0 | 20.2 | 85.2 | 0.009 |
| | Placebo | 1667 | 25 | 1.5 | 1.0 | 2.2 | - | - | - | - |
| G2 | HRV | 1666 | 14 | 0.8 | 0.5 | 1.4 | 68.2 | 40.8 | 83.9 | <0.001 |
| | Placebo | 1667 | 44 | 2.6 | 1.9 | 3.5 | - | - | - | - |
| G3 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 66.6 | -315.4 | 99.4 | 0.625 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| G9 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| GX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 83.3 | -37.5 | 99.6 | 0.125 |
| | Placebo | 1667 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| P4 | HRV | 1666 | 15 | 0.9 | 0.5 | 1.5 | 65.9 | 37.5 | 82.4 | <0.001 |
| | Placebo | 1667 | 44 | 2.6 | 1.9 | 3.5 | - | - | - | - |
| P8WT | HRV | 1666 | 10 | 0.6 | 0.3 | 1.1 | 67.7 | 32.4 | 85.9 | 0.001 |
| | Placebo | 1667 | 31 | 1.9 | 1.3 | 2.6 | - | - | - | - |
| PX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | -0.1 | -7754.4 | 98.7 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 16 | 1.0 | 0.5 | 1.6 | 70.9 | 48.5 | 84.4 | <0.001 |
| | Placebo | 1667 | 55 | 3.3 | 2.5 | 4.3 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
WT = Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 131 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by combination of G and P types (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 60.0 | 5.1 | 84.8 | 0.036 |
| | Placebo | 1667 | 20 | 1.2 | 0.7 | 1.8 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 80.0 | -78.8 | 99.6 | 0.219 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G2+P4 | HRV | 1666 | 14 | 0.8 | 0.5 | 1.4 | 65.8 | 36.0 | 82.8 | <0.001 |
| | Placebo | 1667 | 41 | 2.5 | 1.8 | 3.3 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 66.6 | -315.4 | 99.4 | 0.625 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| G9+P8WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |

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

## Table 132 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by RV type (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1666 | 22 | 1.3 | 0.8 | 2.0 | 56.8 | 27.5 | 75.1 | <0.001 |
| | Placebo | 1667 | 51 | 3.1 | 2.3 | 4.0 | - | - | - | - |
| G2 | HRV | 1666 | 46 | 2.8 | 2.0 | 3.7 | 58.2 | 40.5 | 71.0 | <0.001 |
| | Placebo | 1667 | 110 | 6.6 | 5.5 | 7.9 | - | - | - | - |
| G3 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 83.3 | 25.1 | 98.2 | 0.013 |
| | Placebo | 1667 | 12 | 0.7 | 0.4 | 1.3 | - | - | - | - |
| G9 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 80.0 | -78.8 | 99.6 | 0.219 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| GX | HRV | 1666 | 6 | 0.4 | 0.1 | 0.8 | 25.0 | -146.6 | 78.5 | 0.791 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| P4 | HRV | 1666 | 47 | 2.8 | 2.1 | 3.7 | 58.4 | 41.0 | 71.0 | <0.001 |
| | Placebo | 1667 | 113 | 6.8 | 5.6 | 8.1 | - | - | - | - |
| P8WT | HRV | 1666 | 26 | 1.6 | 1.0 | 2.3 | 58.7 | 33.8 | 74.9 | <0.001 |
| | Placebo | 1667 | 63 | 3.8 | 2.9 | 4.8 | - | - | - | - |
| P9 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| PX | HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | -300.2 | -19610.8 | 60.4 | 0.375 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 54 | 3.2 | 2.4 | 4.2 | 59.7 | 44.3 | 71.2 | <0.001 |
| | Placebo | 1667 | 134 | 8.0 | 6.8 | 9.4 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 133 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by combination of G and P types (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1666 | 20 | 1.2 | 0.7 | 1.8 | 52.4 | 17.0 | 73.5 | 0.007 |
| | Placebo | 1667 | 42 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 80.0 | 6.1 | 97.9 | 0.039 |
| | Placebo | 1667 | 10 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| G2+P4 | HRV | 1666 | 46 | 2.8 | 2.0 | 3.7 | 57.0 | 38.7 | 70.2 | <0.001 |
| | Placebo | 1667 | 107 | 6.4 | 5.3 | 7.7 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 90.9 | 37.4 | 99.8 | 0.006 |
| | Placebo | 1667 | 11 | 0.7 | 0.3 | 1.2 | - | - | - | - |
| G9+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 80.0 | -78.8 | 99.6 | 0.219 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |

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

## Table 134 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from Dose 1 up to Visit 7 (Total vaccinated cohort)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 75 | 2306.33 | 0.033 | 0.026 | 0.041 | 0.047 | 0.034 | 0.062 |
| Placebo | 1667 | 176 | 2205.30 | 0.080 | 0.069 | 0.093 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1666 | 22 | 2342.64 | 0.009 | 0.006 | 0.014 | 0.013 | 0.006 | 0.020 |
| Placebo | 1667 | 51 | 2305.74 | 0.022 | 0.017 | 0.029 | . | . | . |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | |
| HRV | 1666 | 54 | 2314.54 | 0.023 | 0.018 | 0.030 | 0.037 | 0.025 | 0.049 |
| Placebo | 1667 | 134 | 2228.82 | 0.060 | 0.051 | 0.071 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 25 | 2336.73 | 0.011 | 0.007 | 0.016 | 0.023 | 0.014 | 0.032 |
| Placebo | 1667 | 76 | 2285.13 | 0.033 | 0.027 | 0.042 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1666 | 9 | 2348.32 | 0.004 | 0.002 | 0.007 | 0.007 | 0.002 | 0.012 |
| Placebo | 1667 | 25 | 2321.74 | 0.011 | 0.007 | 0.016 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1666 | 16 | 2339.57 | 0.007 | 0.004 | 0.011 | 0.017 | 0.010 | 0.025 |
| Placebo | 1667 | 55 | 2294.87 | 0.024 | 0.018 | 0.031 | . | . | . |

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

**Table 135 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 7 by Cox method (Total vaccinated cohort)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 75 | 2306.33 | 0.03 | 0.03 | 0.04 | 59.35 | 46.73 | 68.97 | <0.001 |
| Placebo | 1667 | 176 | 2205.30 | 0.08 | 0.07 | 0.09 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1666 | 22 | 2342.64 | 0.01 | 0.01 | 0.01 | 57.76 | 30.37 | 74.38 | <0.001 |
| Placebo | 1667 | 51 | 2305.74 | 0.02 | 0.02 | 0.03 | - | - | - | - |
| **Any RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1666 | 54 | 2314.54 | 0.02 | 0.02 | 0.03 | 61.17 | 46.74 | 71.69 | <0.001 |
| Placebo | 1667 | 134 | 2228.82 | 0.06 | 0.05 | 0.07 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 25 | 2336.73 | 0.01 | 0.01 | 0.02 | 67.99 | 49.70 | 79.63 | <0.001 |
| Placebo | 1667 | 76 | 2285.13 | 0.03 | 0.03 | 0.04 | - | - | - | - |
| **Severe RVGE of G1 WT** | | | | | | | | | | |
| HRV | 1666 | 9 | 2348.32 | 0.00 | 0.00 | 0.01 | 64.66 | 24.28 | 83.50 | 0.007 |
| Placebo | 1667 | 25 | 2321.74 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1666 | 16 | 2339.57 | 0.01 | 0.00 | 0.01 | 71.50 | 50.27 | 83.67 | <0.001 |
| Placebo | 1667 | 55 | 2294.87 | 0.02 | 0.02 | 0.03 | - | - | - | - |

WT = Wild Type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)

### 11.5.2.4. Vaccine efficacy against hospitalisation due to RV

**Table 136 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | 80.9 | 43.5 | 95.2 | <0.001 |
| Placebo | 1667 | 21 | 1.3 | 0.8 | 1.9 | - | - | - | - |

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

**Table 137 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 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 36 | 2.2 | 1.5 | 3.0 | 64.3 | 47.3 | 76.3 | <0.001 |
| Placebo | 1667 | 101 | 6.1 | 5.0 | 7.3 | - | - | - | - |

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

### 11.5.2.5. Vaccine efficacy against all cause GE

**Table 138 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 849 | 51.0 | 48.5 | 53.4 | 2.0 | -7.8 | 11.0 | 0.691 |
| Placebo | 1667 | 867 | 52.0 | 49.6 | 54.4 | - | - | - | - |

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

**Table 139 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 210 | 12.6 | 11.0 | 14.3 | 12.4 | -5.8 | 27.6 | 0.174 |
| Placebo | 1667 | 240 | 14.4 | 12.7 | 16.2 | - | - | - | - |

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

## Table 140 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 50 | 3.0 | 2.2 | 3.9 | 45.6 | 22.4 | 62.3 | <0.001 |
| Placebo | 1667 | 92 | 5.5 | 4.5 | 6.7 | - | - | - | - |

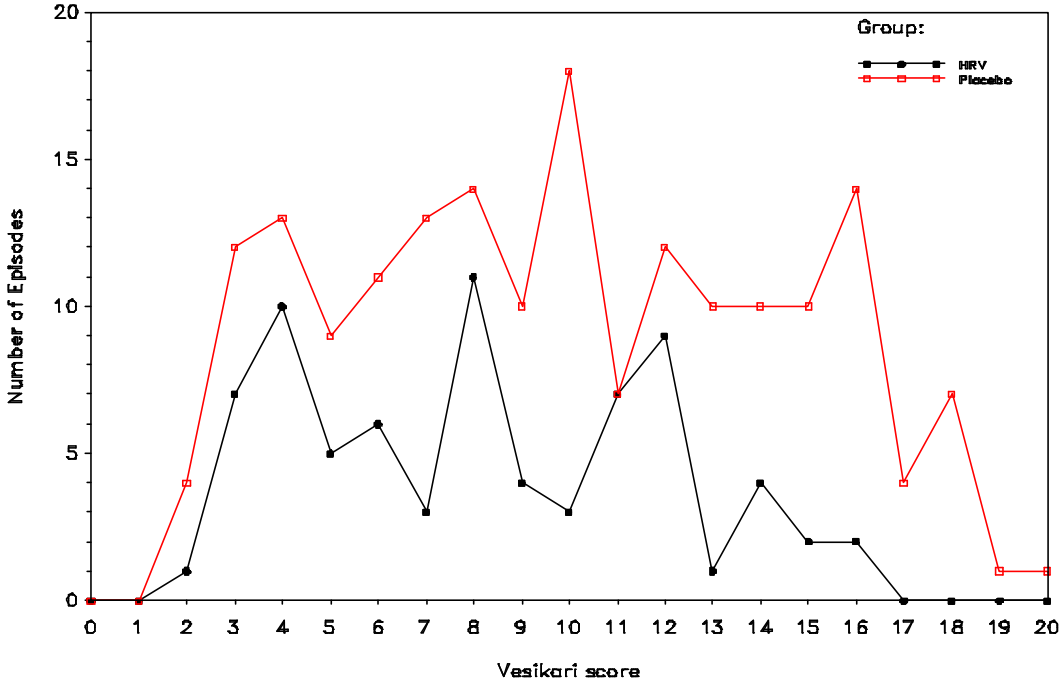
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 141 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 378 | 22.7 | 20.7 | 24.8 | 9.1 | -4.8 | 21.1 | 0.192 |
| Placebo | 1667 | 416 | 25.0 | 22.9 | 27.1 | - | - | - | - |

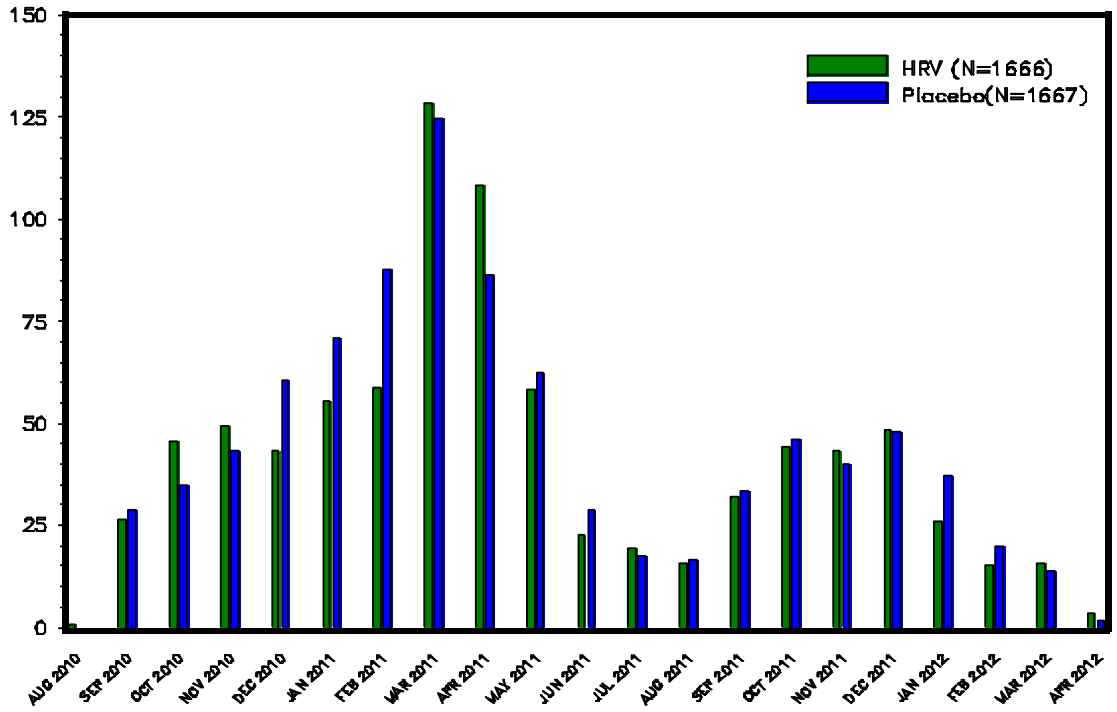
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 21 Distribution of Vesikari score for RV GE episodes reported from Dose 1 up to Visit 7 (Total vaccinated cohort)**



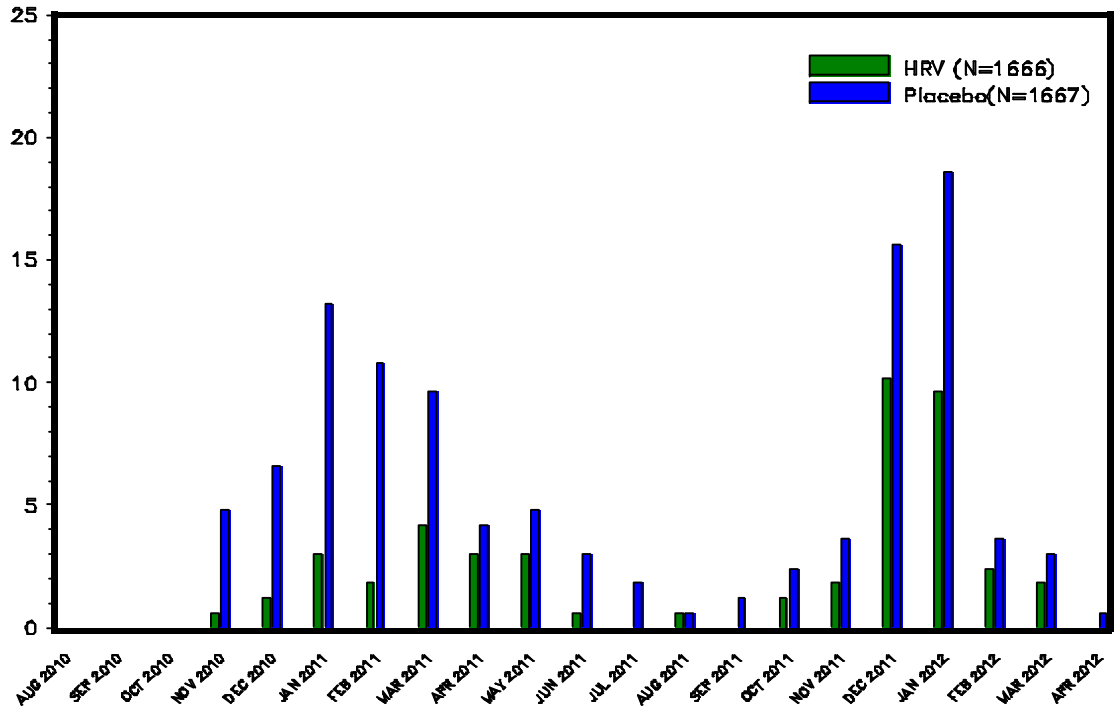

X axis = Score for each episodes computed based on the Vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 22 Seasonal distribution of GE episodes reported from Dose 1 up to Visit 7 for HRV group and placebo group (Total vaccinated cohort)**



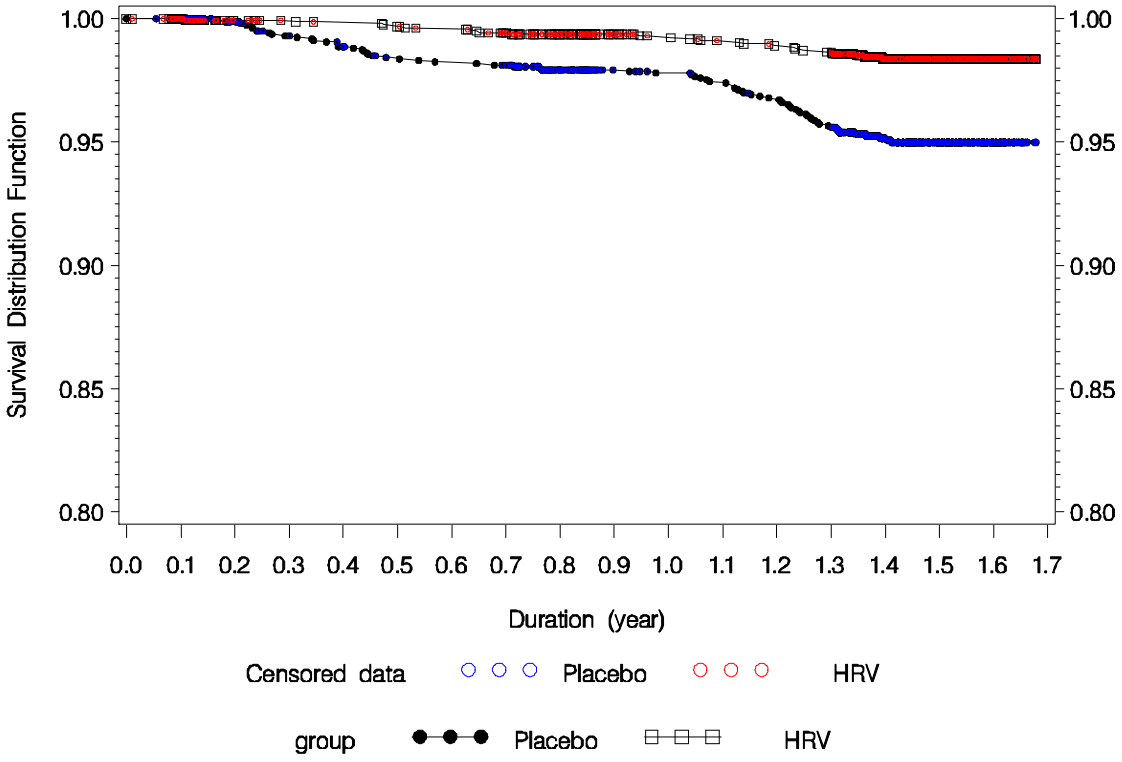

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in each group

**Figure 23 Seasonal distribution of RVGE episodes reported from Dose 1 up to Visit 7 for HRV group and placebo group (Total vaccinated cohort)**



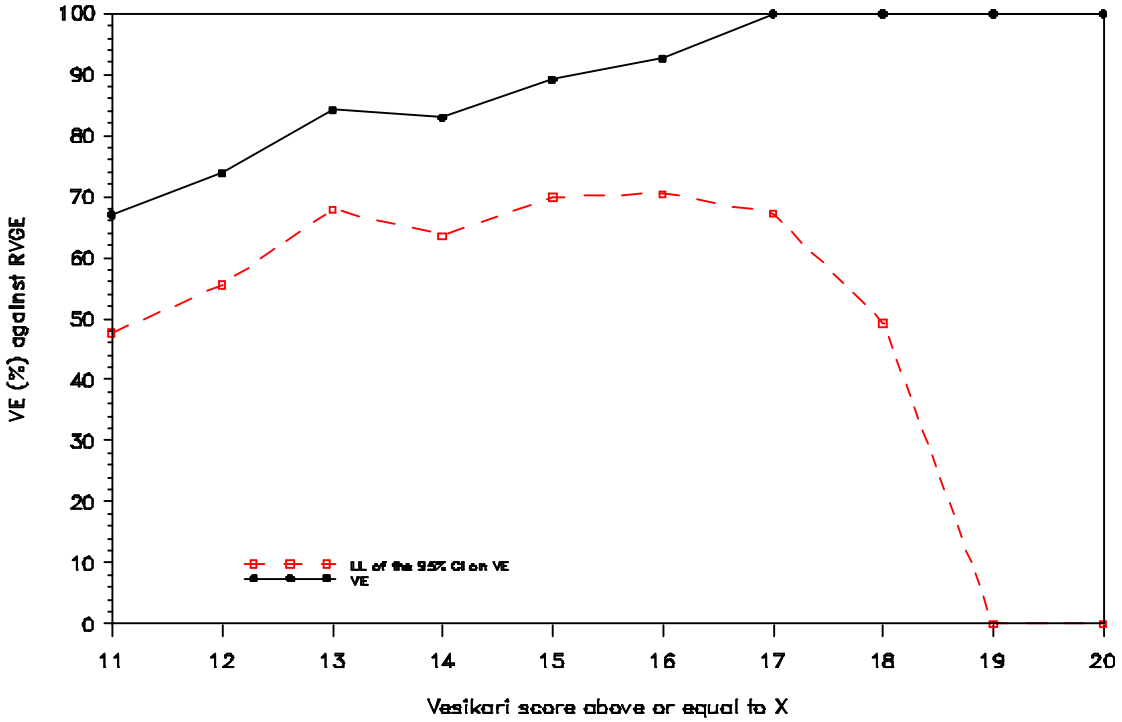

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in each group

**Figure 24 The Kaplan Meier curve for severe RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)**



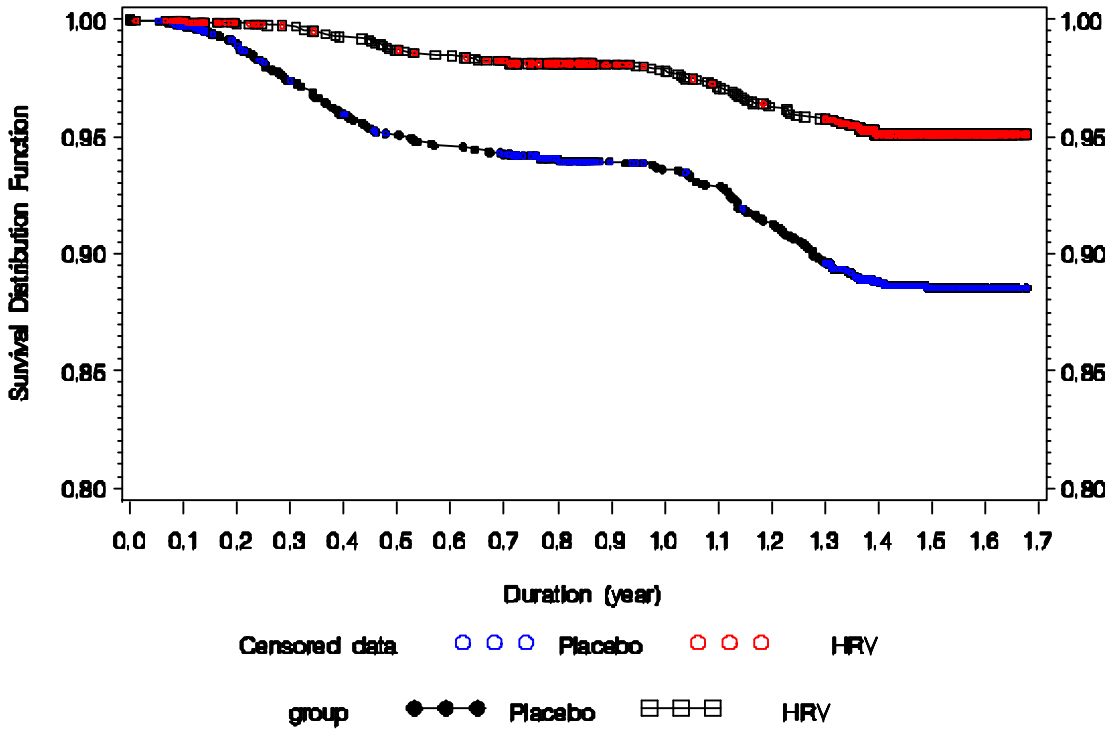

Y Axis is cut at 0.8

**Figure 25 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from Dose 1 up to Visit 7 (Total vaccinated cohort)**



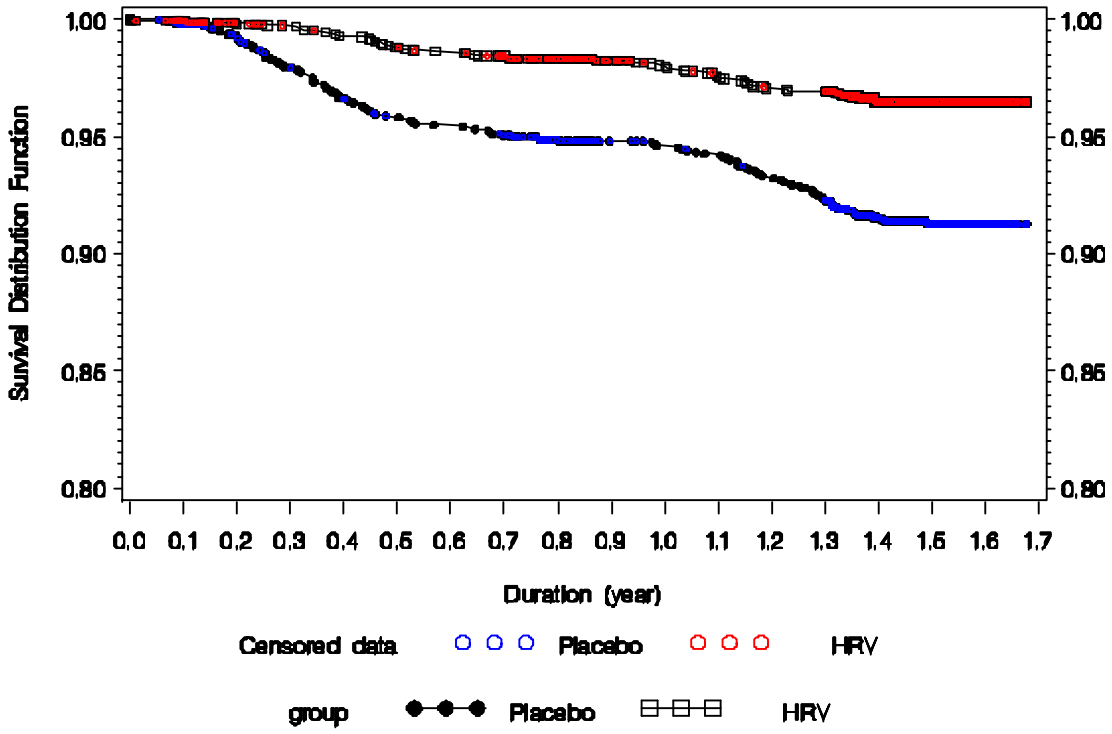

X Axis is cut at 11
Y Axis is cut at 0
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 26 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)**



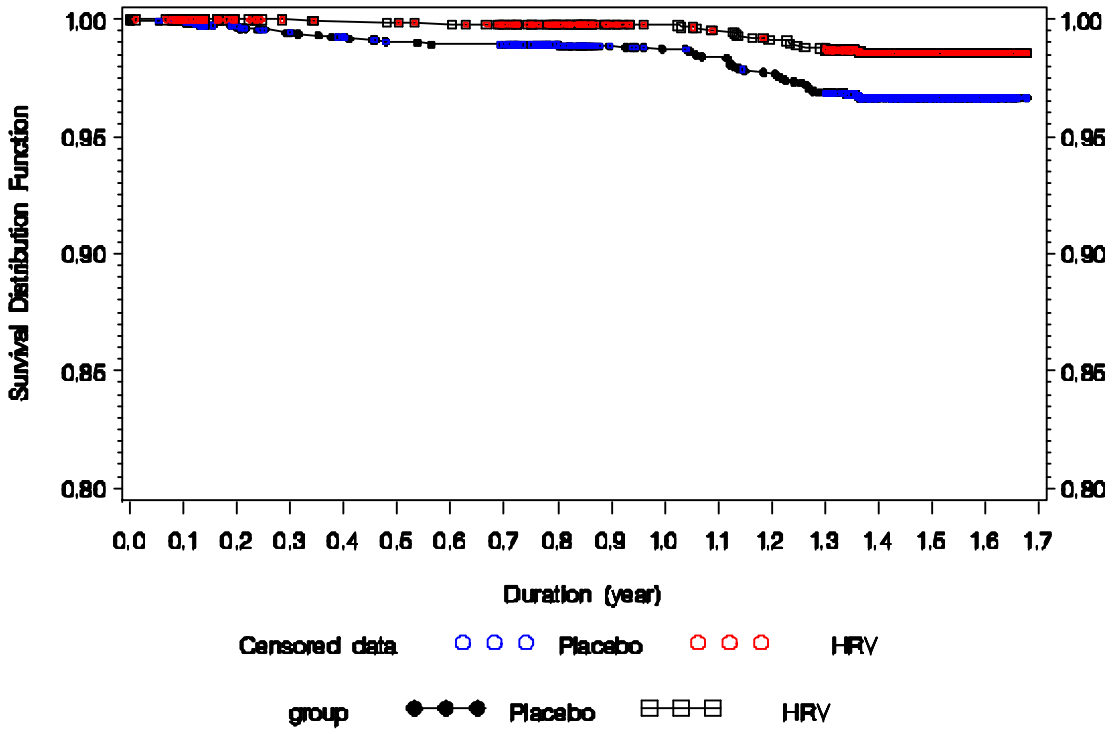

Y Axis is cut at 0.8

**Figure 27 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 7 (Total vaccinated cohort)**



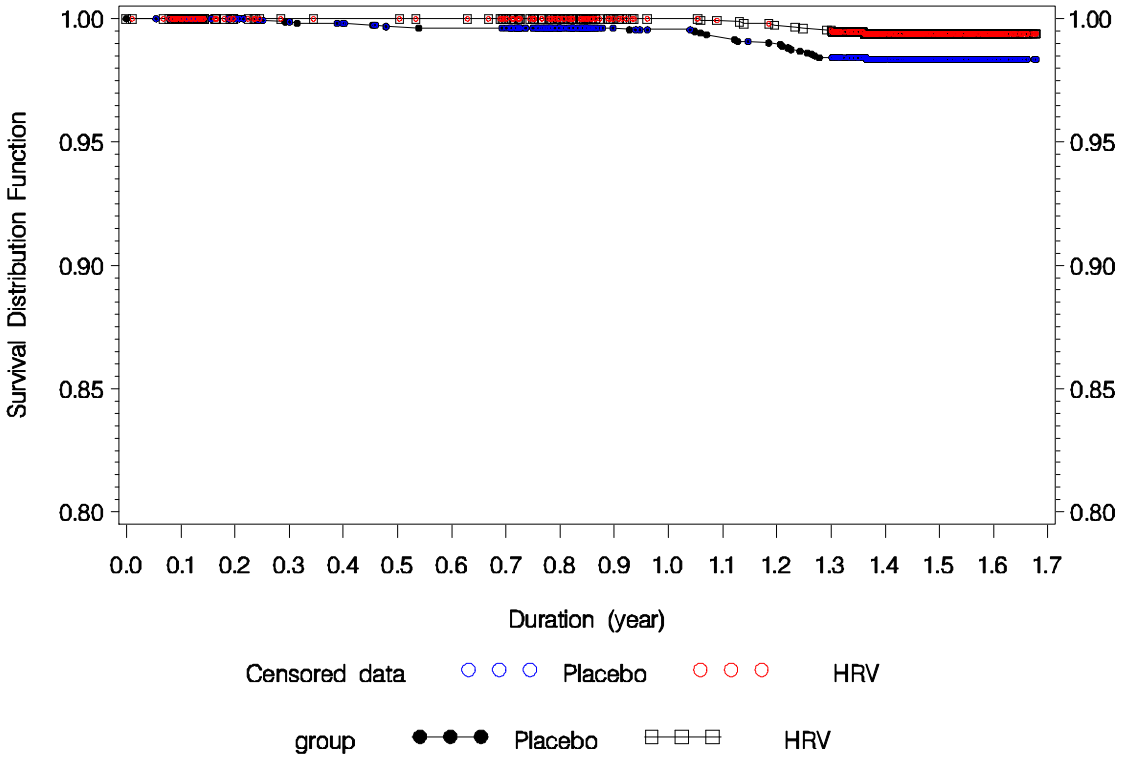

Y Axis is cut at 0.8

**Figure 28 The Kaplan Meier curve for any RV GE due to G1 wild type from Dose 1 up to Visit 7 (Total vaccinated cohort)**



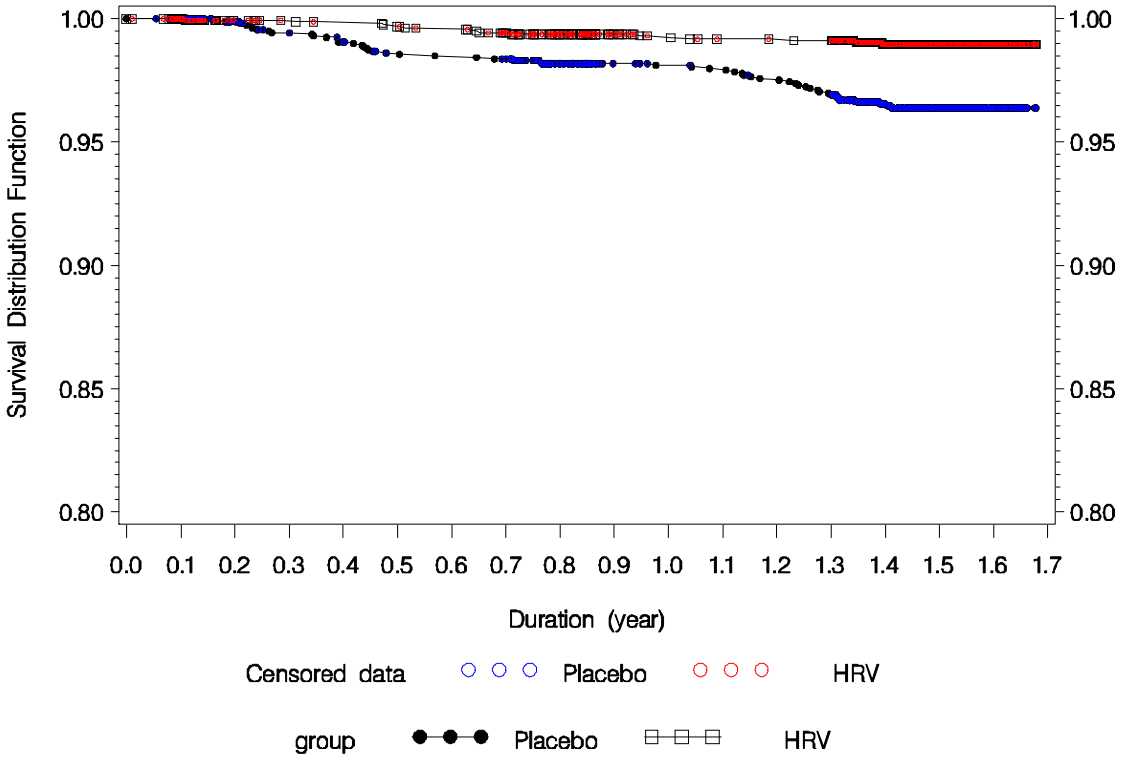

Y Axis is cut at 0.8

**Figure 29 The Kaplan Meier curve for severe RV GE due to G1 wild type from Dose 1 up to Visit 7 (Total vaccinated cohort)**




Y Axis is cut at 0.8

**Figure 30 The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from Dose 1 up to Visit 7 (Total vaccinated cohort)**




Y Axis is cut at 0.8

## 11.5.3. Characterization of GE episodes from Dose 1 up to Visit 6

### Table 142 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 N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 948 | 56.9 | 927 | 55.6 | 1875 | 56.3 |
| | 1 | 493 | 29.6 | 499 | 29.9 | 992 | 29.8 |
| | 2 | 148 | 8.9 | 162 | 9.7 | 310 | 9.3 |
| | 3 | 48 | 2.9 | 48 | 2.9 | 96 | 2.9 |
| | 4 | 19 | 1.1 | 16 | 1.0 | 35 | 1.1 |
| | 5 | 9 | 0.5 | 7 | 0.4 | 16 | 0.5 |
| | 6 | 0 | 0.0 | 6 | 0.4 | 6 | 0.2 |
| | 7 | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| | Any | 718 | 43.1 | 740 | 44.4 | 1458 | 43.7 |
| RVGE | 0 | 1636 | 98.2 | 1570 | 94.2 | 3206 | 96.2 |
| | 1 | 30 | 1.8 | 94 | 5.6 | 124 | 3.7 |
| | 2 | 0 | 0.0 | 3 | 0.2 | 3 | 0.1 |
| | Any | 30 | 1.8 | 97 | 5.8 | 127 | 3.8 |
| Severe GE | 0 | 1524 | 91.5 | 1514 | 90.8 | 3038 | 91.1 |
| | 1 | 132 | 7.9 | 139 | 8.3 | 271 | 8.1 |
| | 2 | 8 | 0.5 | 12 | 0.7 | 20 | 0.6 |
| | 3 | 2 | 0.1 | 2 | 0.1 | 4 | 0.1 |
| | Any | 142 | 8.5 | 153 | 9.2 | 295 | 8.9 |
| Severe RVGE | 0 | 1656 | 99.4 | 1634 | 98.0 | 3290 | 98.7 |
| | 1 | 10 | 0.6 | 33 | 2.0 | 43 | 1.3 |
| | Any | 10 | 0.6 | 33 | 2.0 | 43 | 1.3 |

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

### Table 143 Number of GE episodes reported from Dose 1 up to Visit 6 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| **Event** | **Severity using 20 point Vesikari scale** | **n** | **%** | **n** | **%** |
| GE | Mild (1-6) | 613 | 57.8 | 652 | 58.4 |
| | Moderate (7-10) | 285 | 26.9 | 288 | 25.8 |
| | Severe (≥11) | 154 | 14.5 | 169 | 15.1 |
| | Unknown | 9 | 0.8 | 7 | 0.6 |
| | Any | 1052 | 99.2 | 1109 | 99.4 |
| RVGE | Mild (1-6) | 12 | 40.0 | 32 | 32.0 |
| | Moderate (7-10) | 8 | 26.7 | 35 | 35.0 |
| | Severe (≥11) | 10 | 33.3 | 33 | 33.0 |
| | Any | 30 | 100 | 100 | 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

## Table 144 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 6 (Total vaccinated cohort)

| | HRV N' = 1061 | | Placebo N' = 1116 | | Total N' = 2177 | |
|---|---|---|---|---|---|---|
| **Categories** | **n** | **%** | **n** | **%** | **n** | **%** |
| No stool results available | 161 | 15.2 | 146 | 13.1 | 307 | 14.1 |
| no stools collected | 161 | 15.2 | 146 | 13.1 | 307 | 14.1 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 145 Percentage of subjects with RV GE episodes from Dose 1 up to Visit 6 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** |
| Any | 30 | 1.8 | 97 | 5.8 |
| G1 WT | 3 | 0.2 | 18 | 1.1 |
| G2 | 24 | 1.4 | 73 | 4.4 |
| G3 | 1 | 0.1 | 8 | 0.5 |
| G9 | 0 | 0.0 | 1 | 0.1 |
| GX | 2 | 0.1 | 2 | 0.1 |
| P4 | 24 | 1.4 | 73 | 4.4 |
| P8 WT | 4 | 0.2 | 25 | 1.5 |
| PX | 3 | 0.2 | 1 | 0.1 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 146 Percentage of subjects with severe RV GE episodes from Dose 1 up to Visit 6 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** |
| Any | 10 | 0.6 | 33 | 2.0 |
| G1 WT | 0 | 0.0 | 6 | 0.4 |
| G2 | 8 | 0.5 | 28 | 1.7 |
| G3 | 1 | 0.1 | 2 | 0.1 |
| GX | 1 | 0.1 | 0 | 0.0 |
| P4 | 8 | 0.5 | 26 | 1.6 |
| P8 WT | 2 | 0.1 | 7 | 0.4 |
| PX | 1 | 0.1 | 1 | 0.1 |

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 severe RV GE episode whatever the serotype
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 147 Number of RV GE episodes reported from Dose 1 up to Visit 6, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=30 | | Placebo N'=100 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 3 | 3.00 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 1.00 |
| G1WT+P4 | 0 | 0.00 | 1 | 1.00 |
| G1WT+P8WT | 2 | 6.67 | 14 | 14.00 |
| G1WT+PX | 1 | 3.33 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.00 |
| G2+P4 | 23 | 76.67 | 69 | 69.00 |
| G2+P4+P8WT | 1 | 3.33 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.00 |
| G3+P8WT | 1 | 3.33 | 7 | 7.00 |
| G9+P8WT | 0 | 0.00 | 1 | 1.00 |
| GX | 0 | 0.00 | 1 | 1.00 |
| GX+P8WT | 0 | 0.00 | 1 | 1.00 |
| GX+PX | 2 | 6.67 | 0 | 0.00 |

WT=Wild Type
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 to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 148 Number of severe RV GE episodes reported from Dose 1 up to Visit 6, by G and P type (Total vaccinated cohort )

| Serotype | HRV N'= 10 | | Placebo N'=33 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 3.03 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 3.03 |
| G1WT+P8WT | 0 | 0.00 | 4 | 12.12 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 3.03 |
| G2+P4 | 7 | 70.00 | 24 | 72.73 |
| G2+P4+P8WT | 1 | 10.00 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 3.03 |
| G3+P8WT | 1 | 10.00 | 1 | 3.03 |
| GX+PX | 1 | 10.00 | 0 | 0.00 |

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 severe RV GE episodes reported from dose 1 to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 149 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 (Total vaccinated cohort)

| | | HRV N' = 30 | | Placebo N' = 100 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.1 | - | 8.8 | - |
| | SD | 3.9 | - | 4.2 | - |
| | Median | 8.0 | - | 8.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 24 | 80.0 | 63 | 63.0 |
| | 5 | 3 | 10.0 | 14 | 14.0 |
| | more than 5 days | 3 | 10.0 | 23 | 23.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 4 | 13.3 | 15 | 15.0 |
| | 4 to 5 | 13 | 43.3 | 37 | 37.0 |
| | more than 5 | 13 | 43.3 | 48 | 48.0 |
| Duration of vomiting (days) | 0 day | 17 | 56.7 | 49 | 49.0 |
| | 1 day | 4 | 13.3 | 20 | 20.0 |
| | 2 days | 6 | 20.0 | 14 | 14.0 |
| | more than 2 days | 3 | 10.0 | 17 | 17.0 |
| Max number of episodes of vomiting /day | 0 | 17 | 56.7 | 49 | 49.0 |
| | 1 | 2 | 6.7 | 12 | 12.0 |
| | 2 to 4 | 9 | 30.0 | 31 | 31.0 |
| | more than 4 | 2 | 6.7 | 8 | 8.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 8 | 26.7 | 33 | 33.0 |
| | 36.6 to 37.9°C | 13 | 43.3 | 45 | 45.0 |
| | 38.0 to 38.4°C | 6 | 20.0 | 12 | 12.0 |
| | more than 38.4°C | 3 | 10.0 | 10 | 10.0 |
| Treatment | none | 17 | 56.7 | 52 | 52.0 |
| | rehydration | 11 | 36.7 | 34 | 34.0 |
| | hospitalization | 2 | 6.7 | 14 | 14.0 |
| Dehydration | none | 17 | 56.7 | 52 | 52.0 |
| | 1 to 5% | 4 | 13.3 | 12 | 12.0 |
| | more than 5 % | 9 | 30.0 | 36 | 36.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 150 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By G1WT type (Total vaccinated cohort)

| | | HRV N' = 3 | | Placebo N' = 19 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.0 | - | 8.6 | - |
| | SD | 3.6 | - | 3.2 | - |
| | Median | 5.0 | - | 10.0 | - |
| | Minimum | 3.0 | - | 3.0 | - |
| | Maximum | 10.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 100 | 12 | 63.2 |
| | 5 | 0 | 0.0 | 5 | 26.3 |
| | more than 5 days | 0 | 0.0 | 2 | 10.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 33.3 | 0 | 0.0 |
| | 4 to 5 | 1 | 33.3 | 12 | 63.2 |
| | more than 5 | 1 | 33.3 | 7 | 36.8 |
| Duration of vomiting (days) | 0 day | 3 | 100 | 9 | 47.4 |
| | 1 day | 0 | 0.0 | 5 | 26.3 |
| | 2 days | 0 | 0.0 | 2 | 10.5 |
| | more than 2 days | 0 | 0.0 | 3 | 15.8 |
| Max number of episodes of vomiting /day | 0 | 3 | 100 | 9 | 47.4 |
| | 1 | 0 | 0.0 | 2 | 10.5 |
| | 2 to 4 | 0 | 0.0 | 8 | 42.1 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 6 | 31.6 |
| | 36.6 to 37.9°C | 1 | 33.3 | 9 | 47.4 |
| | 38.0 to 38.4°C | 1 | 33.3 | 3 | 15.8 |
| | more than 38.4°C | 1 | 33.3 | 1 | 5.3 |
| Treatment | none | 2 | 66.7 | 10 | 52.6 |
| | rehydration | 1 | 33.3 | 5 | 26.3 |
| | hospitalization | 0 | 0.0 | 4 | 21.1 |
| Dehydration | none | 2 | 66.7 | 10 | 52.6 |
| | 1 to 5% | 1 | 33.3 | 3 | 15.8 |
| | more than 5 % | 0 | 0.0 | 6 | 31.6 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 151 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By G2 type (Total vaccinated cohort)

| | | HRV N' = 24 | | Placebo N' = 75 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.2 | - | 9.1 | - |
| | SD | 4.0 | - | 4.6 | - |
| | Median | 8.0 | - | 8.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 20 | 83.3 | 46 | 61.3 |
| | 5 | 2 | 8.3 | 8 | 10.7 |
| | more than 5 days | 2 | 8.3 | 21 | 28.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 3 | 12.5 | 13 | 17.3 |
| | 4 to 5 | 11 | 45.8 | 25 | 33.3 |
| | more than 5 | 10 | 41.7 | 37 | 49.3 |
| Duration of vomiting (days) | 0 day | 13 | 54.2 | 36 | 48.0 |
| | 1 day | 4 | 16.7 | 15 | 20.0 |
| | 2 days | 4 | 16.7 | 12 | 16.0 |
| | more than 2 days | 3 | 12.5 | 12 | 16.0 |
| Max number of episodes of vomiting /day | 0 | 13 | 54.2 | 36 | 48.0 |
| | 1 | 2 | 8.3 | 6 | 8.0 |
| | 2 to 4 | 8 | 33.3 | 25 | 33.3 |
| | more than 4 | 1 | 4.2 | 8 | 10.7 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 8 | 33.3 | 23 | 30.7 |
| | 36.6 to 37.9°C | 10 | 41.7 | 33 | 44.0 |
| | 38.0 to 38.4°C | 5 | 20.8 | 10 | 13.3 |
| | more than 38.4°C | 1 | 4.2 | 9 | 12.0 |
| Treatment | none | 12 | 50.0 | 39 | 52.0 |
| | rehydration | 10 | 41.7 | 25 | 33.3 |
| | hospitalization | 2 | 8.3 | 11 | 14.7 |
| Dehydration | none | 12 | 50.0 | 39 | 52.0 |
| | 1 to 5% | 3 | 12.5 | 7 | 9.3 |
| | more than 5 % | 9 | 37.5 | 29 | 38.7 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 152 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By G3 type (Total vaccinated cohort)

| | | HRV N' = 1 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 11.0 | - | 8.8 | - |
| | SD | 0.0 | - | 4.2 | - |
| | Median | 11.0 | - | 8.5 | - |
| | Minimum | 11.0 | - | 2.0 | - |
| | Maximum | 11.0 | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 5 | 62.5 |
| | 5 | 0 | 0.0 | 1 | 12.5 |
| | more than 5 days | 0 | 0.0 | 2 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 12.5 |
| | 4 to 5 | 0 | 0.0 | 4 | 50.0 |
| | more than 5 | 1 | 100 | 3 | 37.5 |
| Duration of vomiting (days) | 0 day | 0 | 0.0 | 3 | 37.5 |
| | 1 day | 0 | 0.0 | 2 | 25.0 |
| | 2 days | 1 | 100 | 2 | 25.0 |
| | more than 2 days | 0 | 0.0 | 1 | 12.5 |
| Max number of episodes of vomiting /day | 0 | 0 | 0.0 | 3 | 37.5 |
| | 1 | 0 | 0.0 | 3 | 37.5 |
| | 2 to 4 | 1 | 100 | 1 | 12.5 |
| | more than 4 | 0 | 0.0 | 1 | 12.5 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 3 | 37.5 |
| | 36.6 to 37.9°C | 0 | 0.0 | 4 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 1 | 100 | 1 | 12.5 |
| Treatment | none | 1 | 100 | 4 | 50.0 |
| | rehydration | 0 | 0.0 | 4 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 4 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 12.5 |
| | more than 5 % | 0 | 0.0 | 3 | 37.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 153 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By GX type (Total vaccinated cohort)

| | | HRV N' = 2 | | Placebo N' = 2 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.5 | - | 9.0 | - |
| | SD | 4.9 | - | 1.4 | - |
| | Median | 8.5 | - | 9.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 10.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 0 | 0.0 | 2 | 100 |
| | 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 days | 1 | 50.0 | 0 | 0.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 50.0 |
| | 4 to 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 | 1 | 50.0 | 1 | 50.0 |
| Duration of vomiting (days) | 0 day | 1 | 50.0 | 0 | 0.0 |
| | 1 day | 0 | 0.0 | 1 | 50.0 |
| | 2 days | 1 | 50.0 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 1 | 50.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 50.0 | 0 | 0.0 |
| | 1 | 0 | 0.0 | 1 | 50.0 |
| | 2 to 4 | 0 | 0.0 | 1 | 50.0 |
| | more than 4 | 1 | 50.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 1 | 50.0 |
| | 36.6 to 37.9°C | 2 | 100 | 1 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 0 | 0.0 |
| Treatment | none | 2 | 100 | 1 | 50.0 |
| | rehydration | 0 | 0.0 | 1 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 2 | 100 | 1 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 0 | 0.0 |
| | more than 5 % | 0 | 0.0 | 1 | 50.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain

## Table 154 Characteristics of the GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 (Total vaccinated cohort)

| | | HRV N' = 1061 | | Placebo N' = 1116 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.3 | - | 6.5 | - |
| | SD | 3.6 | - | 3.7 | - |
| | Median | 5.0 | - | 6.0 | - |
| | Minimum | 0.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 13 | 1.2 | 10 | 0.9 |
| | 1 to 4 days | 738 | 69.6 | 753 | 67.5 |
| | 5 | 109 | 10.3 | 105 | 9.4 |
| | more than 5 days | 201 | 18.9 | 248 | 22.2 |
| Maximum number of looser than normal stools/day | 0 | 13 | 1.2 | 10 | 0.9 |
| | 1 to 3 | 216 | 20.4 | 191 | 17.1 |
| | 4 to 5 | 505 | 47.6 | 562 | 50.4 |
| | more than 5 | 327 | 30.8 | 353 | 31.6 |
| Duration of vomiting (days) | 0 day | 795 | 74.9 | 835 | 74.8 |
| | 1 day | 127 | 12.0 | 143 | 12.8 |
| | 2 days | 71 | 6.7 | 55 | 4.9 |
| | more than 2 days | 68 | 6.4 | 83 | 7.4 |
| Max number of episodes of vomiting /day | 0 | 795 | 74.9 | 835 | 74.8 |
| | 1 | 84 | 7.9 | 103 | 9.2 |
| | 2 to 4 | 162 | 15.3 | 146 | 13.1 |
| | more than 4 | 20 | 1.9 | 32 | 2.9 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 495 | 46.7 | 517 | 46.3 |
| | 36.6 to 37.9°C | 436 | 41.1 | 449 | 40.2 |
| | 38.0 to 38.4°C | 53 | 5.0 | 68 | 6.1 |
| | more than 38.4°C | 77 | 7.3 | 82 | 7.3 |
| Treatment | none | 731 | 68.9 | 771 | 69.1 |
| | rehydration | 283 | 26.7 | 275 | 24.6 |
| | hospitalization | 47 | 4.4 | 70 | 6.3 |
| Dehydration | none | 731 | 68.9 | 771 | 69.1 |
| | 1 to 5% | 137 | 12.9 | 132 | 11.8 |
| | more than 5 % | 193 | 18.2 | 213 | 19.1 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 155 Duration (in years) of efficacy follow-up period - from Dose 1 up to Visit 6 (Total vaccinated cohort)**

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 1299 | 1293 |
| | Mean | 0.78 | 0.78 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 0.77 | 0.77 |
| | Median | 0.81 | 0.81 |
| | Q3 | 0.85 | 0.84 |
| | Maximum | 1.09 | 1.05 |

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

## 11.5.4. Vaccine efficacy during the period from Dose 1 up to Visit 6

### 11.5.4.1. Vaccine efficacy against severe RV GE

**Table 156 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) 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 | 1666 | 10 | 0.6 | 0.3 | 1.1 | 69.7 | 37.0 | 86.7 | <0.001 |
| Placebo | 1667 | 33 | 2.0 | 1.4 | 2.8 | - | - | - | - |

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

**Table 157 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Severity using Vesikari scale | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| ≥11 | HRV | 1666 | 10 | 0.6 | 0.3 | 1.1 | 69.7 | 37.0 | 86.7 | <0.001 |
| | Placebo | 1667 | 33 | 2.0 | 1.4 | 2.8 | - | - | - | - |
| ≥12 | HRV | 1666 | 7 | 0.4 | 0.2 | 0.9 | 75.8 | 43.7 | 91.1 | <0.001 |
| | Placebo | 1667 | 29 | 1.7 | 1.2 | 2.5 | - | - | - | - |
| ≥13 | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | 85.0 | 49.4 | 97.1 | <0.001 |
| | Placebo | 1667 | 20 | 1.2 | 0.7 | 1.8 | - | - | - | - |
| ≥14 | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | 76.9 | 16.0 | 95.8 | 0.021 |
| | Placebo | 1667 | 13 | 0.8 | 0.4 | 1.3 | - | - | - | - |
| ≥15 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 77.8 | -7.4 | 97.7 | 0.066 |
| | Placebo | 1667 | 9 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| ≥16 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 87.5 | 6.7 | 99.7 | 0.039 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| ≥17 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -51.6 | 100.0 | 0.125 |
| | Placebo | 1667 | 4 | 0.2 | 0.1 | 0.6 | - | - | - | - |
| ≥18 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| ≥19 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| =20 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 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 a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P_value=Two-sided exact p_value conditional to the number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.5.4.2. Vaccine efficacy against any RV GE

**Table 158 Percentage of subjects reporting any 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 | 1666 | 30 | 1.8 | 1.2 | 2.6 | 69.1 | 53.0 | 80.2 | <0.001 |
| Placebo | 1667 | 97 | 5.8 | 4.7 | 7.1 | - | - | - | - |

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

### 11.5.4.3. Vaccine efficacy against circulating RV types

**Table 159 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 15.0 | 100.0 | 0.031 |
| | Placebo | 1667 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| G2 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 71.4 | 35.6 | 88.7 | 0.001 |
| | Placebo | 1667 | 28 | 1.7 | 1.1 | 2.4 | - | - | - | - |
| G3 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 50.0 | -861.0 | 99.2 | 1.000 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| GX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | Und. | Und. | Und. | 1.000 |
| | Placebo | 1667 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |
| P4 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 69.2 | 30.0 | 88.0 | 0.003 |
| | Placebo | 1667 | 26 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| P8WT | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 71.4 | -50.1 | 97.1 | 0.180 |
| | Placebo | 1667 | 7 | 0.4 | 0.2 | 0.9 | - | - | - | - |
| PX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | -0.1 | -7754.4 | 98.7 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 10 | 0.6 | 0.3 | 1.1 | 65.5 | 27.2 | 85.0 | 0.003 |
| | Placebo | 1667 | 29 | 1.7 | 1.2 | 2.5 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain
Und. = Cannot be estimated

**Table 160 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -9.2 | 100.0 | 0.063 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| G2+P4 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 69.2 | 30.0 | 88.0 | 0.003 |
| | Placebo | 1667 | 26 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 50.0 | -861.0 | 99.2 | 1.000 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |

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

## Table 161 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | 83.3 | 42.9 | 96.9 | 0.001 |
| | Placebo | 1667 | 18 | 1.1 | 0.6 | 1.7 | - | - | - | - |
| G2 | HRV | 1666 | 24 | 1.4 | 0.9 | 2.1 | 67.1 | 47.2 | 80.2 | <0.001 |
| | Placebo | 1667 | 73 | 4.4 | 3.4 | 5.5 | - | - | - | - |
| G3 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 87.5 | 6.7 | 99.7 | 0.039 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| G9 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| GX | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | -0.1 | -1280.4 | 92.7 | 1.000 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| P4 | HRV | 1666 | 24 | 1.4 | 0.9 | 2.1 | 67.1 | 47.2 | 80.2 | <0.001 |
| | Placebo | 1667 | 73 | 4.4 | 3.4 | 5.5 | - | - | - | - |
| P8WT | HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | 84.0 | 53.6 | 96.0 | <0.001 |
| | Placebo | 1667 | 25 | 1.5 | 1.0 | 2.2 | - | - | - | - |
| PX | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | -200.2 | -15658.7 | 75.9 | 0.625 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 27 | 1.6 | 1.1 | 2.3 | 67.5 | 49.2 | 79.7 | <0.001 |
| | Placebo | 1667 | 83 | 5.0 | 4.0 | 6.1 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 162 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 86.7 | 42.6 | 98.5 | 0.002 |
| | Placebo | 1667 | 15 | 0.9 | 0.5 | 1.5 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| G2+P4 | HRV | 1666 | 24 | 1.4 | 0.9 | 2.1 | 66.6 | 46.4 | 79.9 | <0.001 |
| | Placebo | 1667 | 72 | 4.3 | 3.4 | 5.4 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 87.5 | 6.7 | 99.7 | 0.039 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| G9+P8WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |

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

## Table 163 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from Dose 1 up to Visit 6 (Total vaccinated cohort)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 30 | 1287.94 | 0.023 | 0.016 | 0.033 | 0.054 | 0.037 | 0.073 |
| Placebo | 1667 | 97 | 1251.20 | 0.078 | 0.064 | 0.095 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1666 | 3 | 1298.17 | 0.002 | 0.001 | 0.007 | 0.012 | 0.005 | 0.020 |
| Placebo | 1667 | 18 | 1284.85 | 0.014 | 0.009 | 0.022 | . | . | . |
| **Any RVGE of Pooled Non-G1** | | | | | | | | | |
| HRV | 1666 | 27 | 1288.92 | 0.021 | 0.014 | 0.031 | 0.045 | 0.029 | 0.062 |
| Placebo | 1667 | 83 | 1257.96 | 0.066 | 0.053 | 0.082 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.008 | 0.004 | 0.014 | 0.018 | 0.008 | 0.029 |
| Placebo | 1667 | 33 | 1280.13 | 0.026 | 0.018 | 0.036 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1666 | 0 | 1299.15 | 0 | Und. | Und. | 0.005 | Und. | Und. |
| Placebo | 1667 | 6 | 1290.20 | 0.005 | 0.002 | 0.010 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.008 | 0.004 | 0.014 | 0.015 | 0.005 | 0.025 |
| Placebo | 1667 | 29 | 1281.92 | 0.023 | 0.016 | 0.033 | . | . | . |

WT= Wild Type
N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(S) in each group
T(Year)= Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Risk difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner
Und. = cannot be estimated

**Table 164 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 6 by Cox method (Total vaccinated cohort)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 30 | 1287.94 | 0.02 | 0.02 | 0.03 | 69.89 | 54.66 | 80.01 | <0.001 |
| Placebo | 1667 | 97 | 1251.20 | 0.08 | 0.06 | 0.09 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1666 | 3 | 1298.17 | 0.00 | 0.00 | 0.01 | 83.45 | 43.84 | 95.12 | 0.004 |
| Placebo | 1667 | 18 | 1284.85 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | | |
| HRV | 1666 | 27 | 1288.92 | 0.02 | 0.01 | 0.03 | 68.19 | 50.90 | 79.40 | <0.001 |
| Placebo | 1667 | 83 | 1257.96 | 0.07 | 0.05 | 0.08 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.01 | 0.00 | 0.01 | 70.01 | 39.15 | 85.22 | <0.001 |
| Placebo | 1667 | 33 | 1280.13 | 0.03 | 0.02 | 0.04 | - | - | - | - |
| **Severe RVGE of G1 WT** | | | | | | | | | | |
| HRV | 1666 | 0 | 1299.15 | 0.00 | Und. | Und. | 100.00 | Und. | 100.00 | 0.994 |
| Placebo | 1667 | 6 | 1290.20 | 0.00 | 0.00 | 0.01 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.01 | 0.00 | 0.01 | 65.83 | 29.88 | 83.35 | 0.003 |
| Placebo | 1667 | 29 | 1281.92 | 0.02 | 0.02 | 0.03 | - | - | - | - |

WT=Wild Type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)
Und. = cannot be estimated

### 11.5.4.4. Vaccine efficacy against hospitalisation due to RV

**Table 165 Percentage of subjects reporting RVGE episode requiring hospitalisation 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 | 1666 | 2 | 0.1 | 0.0 | 0.4 | 85.7 | 37.8 | 98.4 | 0.004 |
| Placebo | 1667 | 14 | 0.8 | 0.5 | 1.4 | - | - | - | - |

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

**Table 166 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 | 1666 | 13 | 0.8 | 0.4 | 1.3 | 72.9 | 49.2 | 86.5 | <0.001 |
| Placebo | 1667 | 48 | 2.9 | 2.1 | 3.8 | - | - | - | - |

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

### 11.5.4.5. Vaccine efficacy against all cause GE

**Table 167 Percentage of subjects reporting all cause of 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 | 1666 | 718 | 43.1 | 40.7 | 45.5 | 2.9 | -7.7 | 12.5 | 0.590 |
| Placebo | 1667 | 740 | 44.4 | 42.0 | 46.8 | - | - | - | - |

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

**Table 168 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) 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 | 1666 | 142 | 8.5 | 7.2 | 10.0 | 7.1 | -17.5 | 26.6 | 0.564 |
| Placebo | 1667 | 153 | 9.2 | 7.8 | 10.7 | - | - | - | - |

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

## Table 169 Percentage of subjects reporting all cause of GE episode requiring hospitalisation 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 | 1666 | 43 | 2.6 | 1.9 | 3.5 | 34.8 | 2.8 | 56.7 | 0.035 |
| Placebo | 1667 | 66 | 4.0 | 3.1 | 5.0 | - | - | - | - |

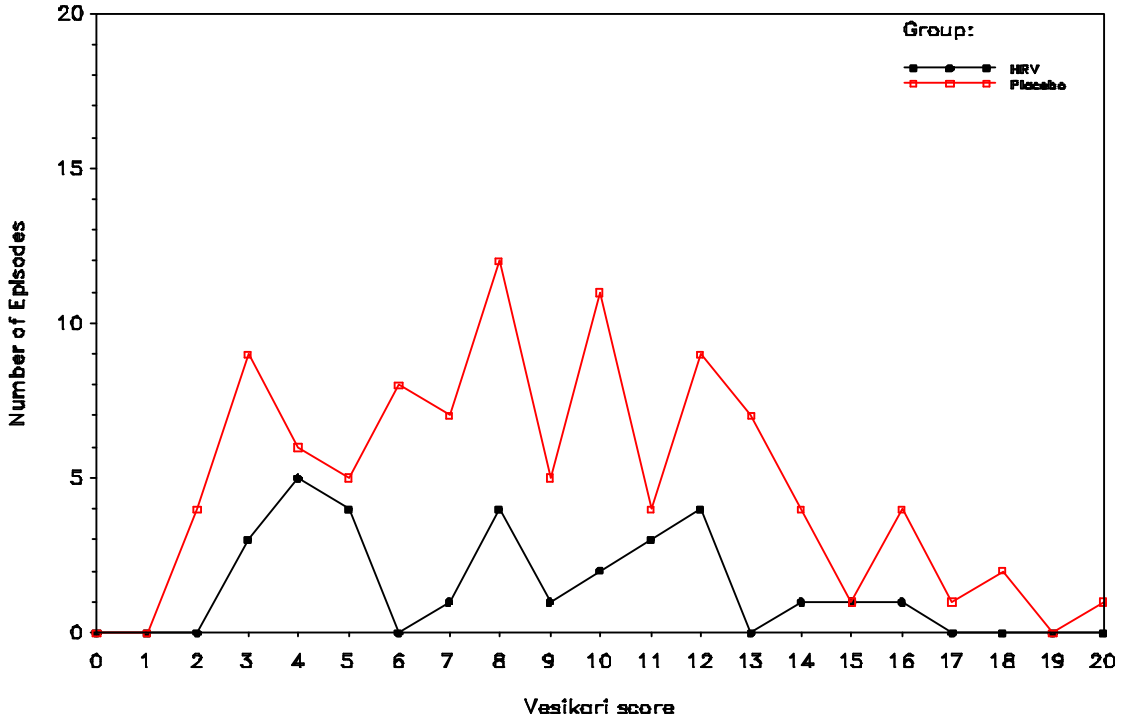
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 170 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of 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 | 1666 | 272 | 16.3 | 14.6 | 18.2 | 7.1 | -9.9 | 21.5 | 0.404 |
| Placebo | 1667 | 293 | 17.6 | 15.8 | 19.5 | - | - | - | - |

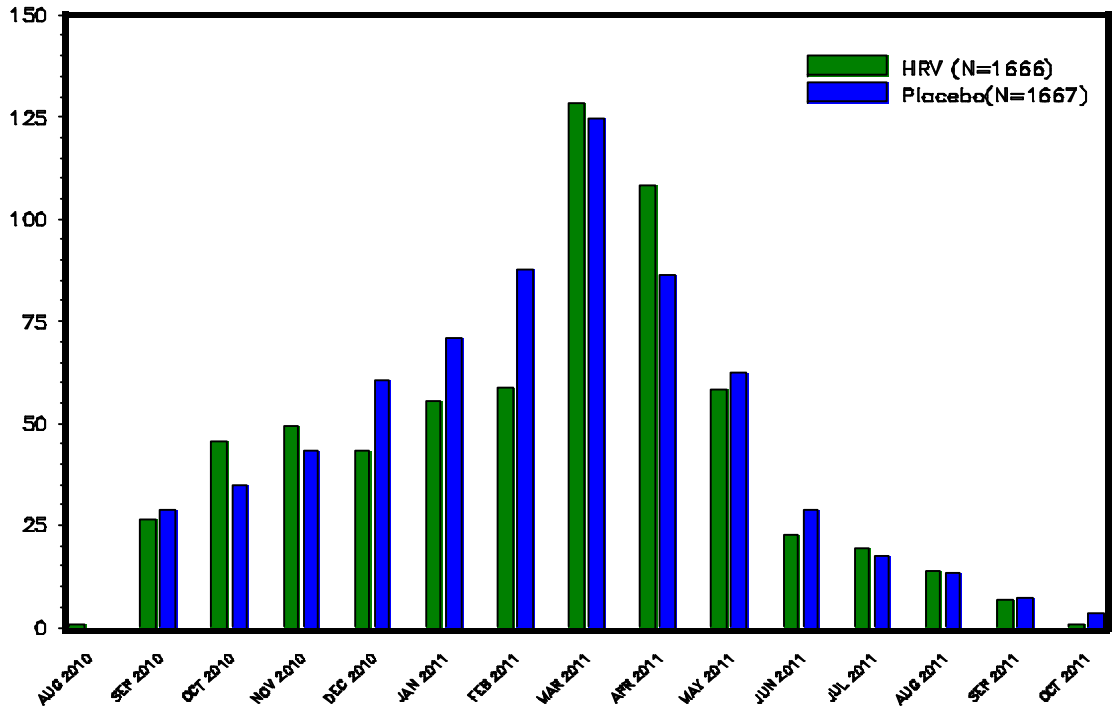
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 31 Distribution of Vesikari score for RV GE episodes reported from Dose 1 up to Visit 6 (Total vaccinated cohort)**



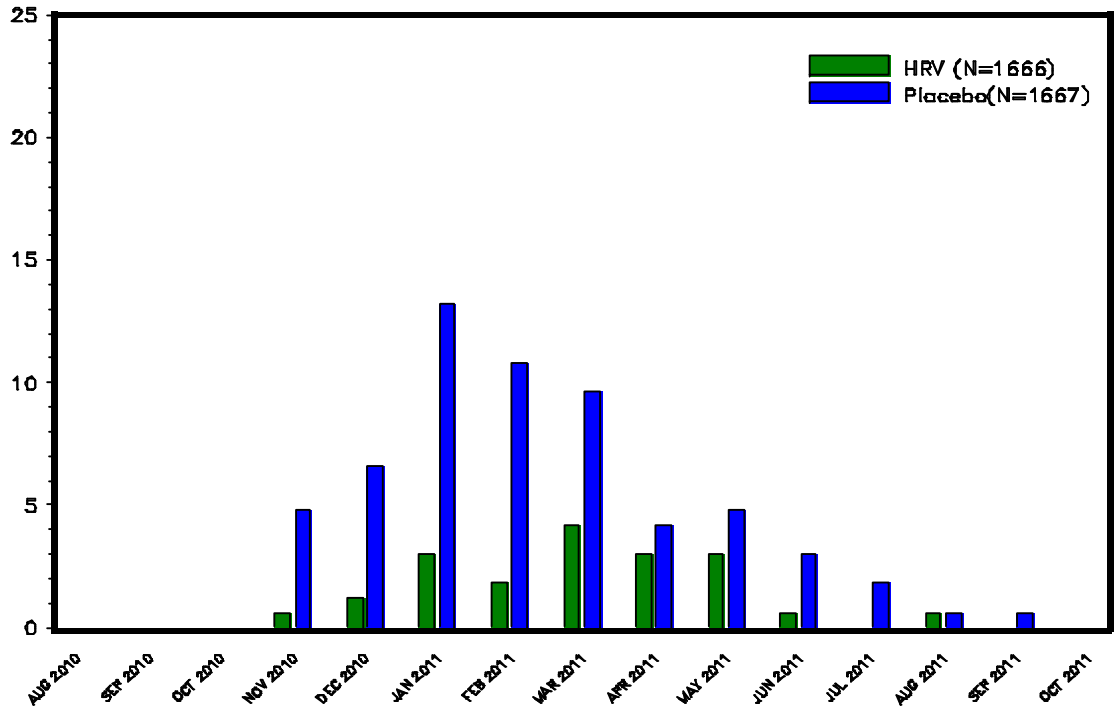

X axis = Score for each episodes computed based on the Vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 32 Seasonal distribution of GE episodes reported from Dose 1 up to Visit 6 for HRV group and placebo group (Total vaccinated cohort)**



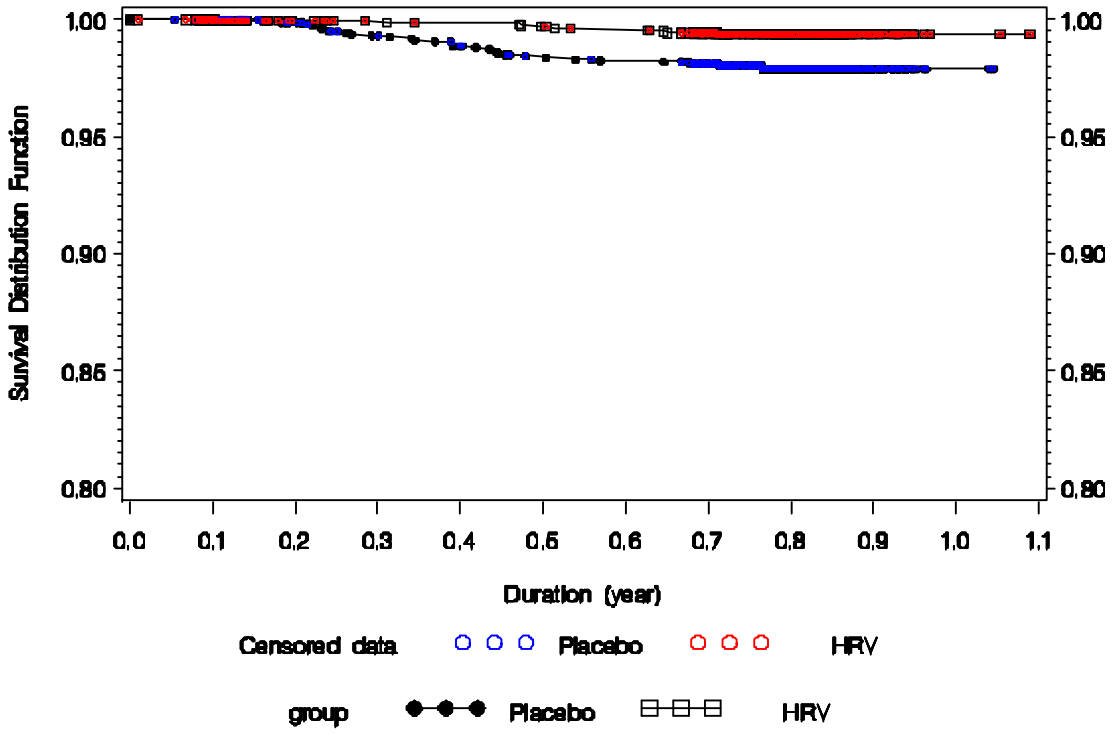

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in the each group

**Figure 33 Seasonal distribution of RVGE episodes reported from Dose 1 up to Visit 6 for HRV group and placebo group (Total vaccinated cohort)**



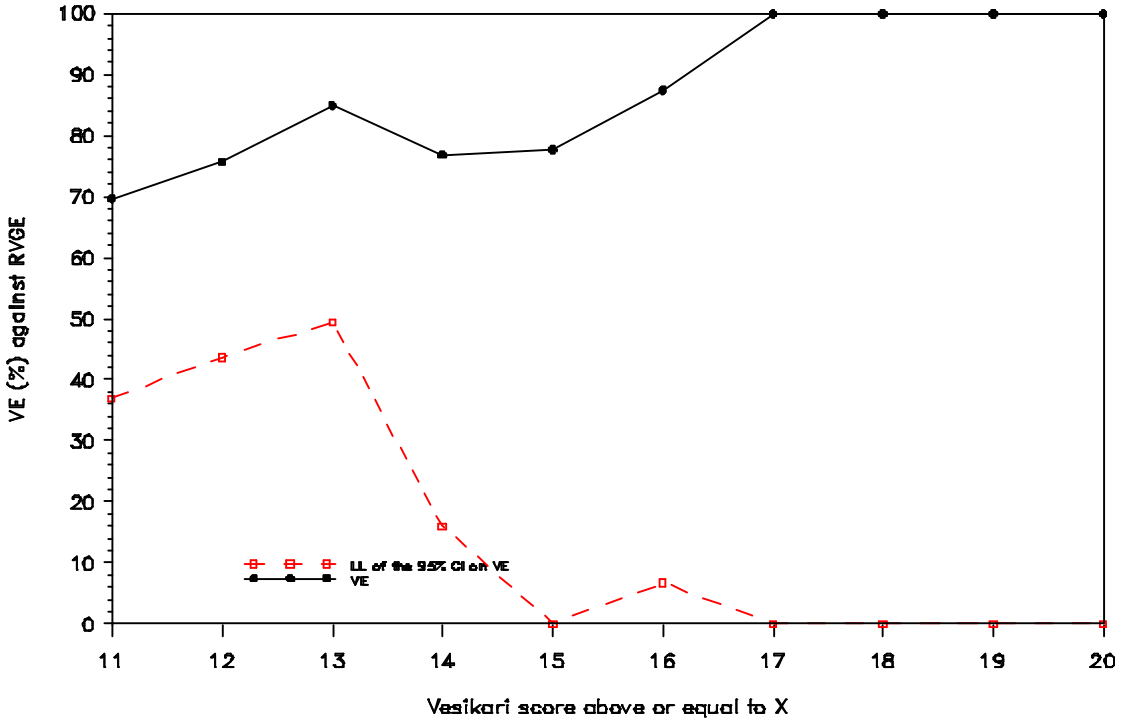

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in the each group

**Figure 34 The Kaplan Meier curve for severe RV GE from Dose 1 up to Visit 6 (Total vaccinated cohort)**



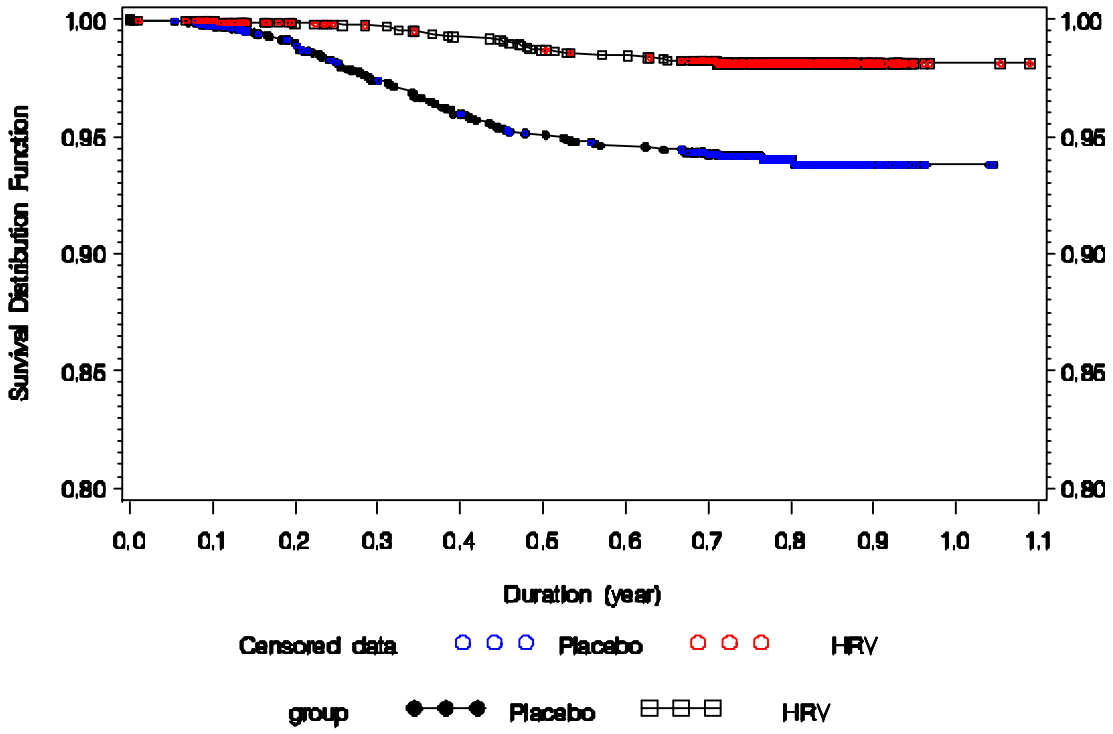

Y Axis is cut at 0.8

**Figure 35 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from dose 1 to visit 6 (Total vaccinated cohort)**



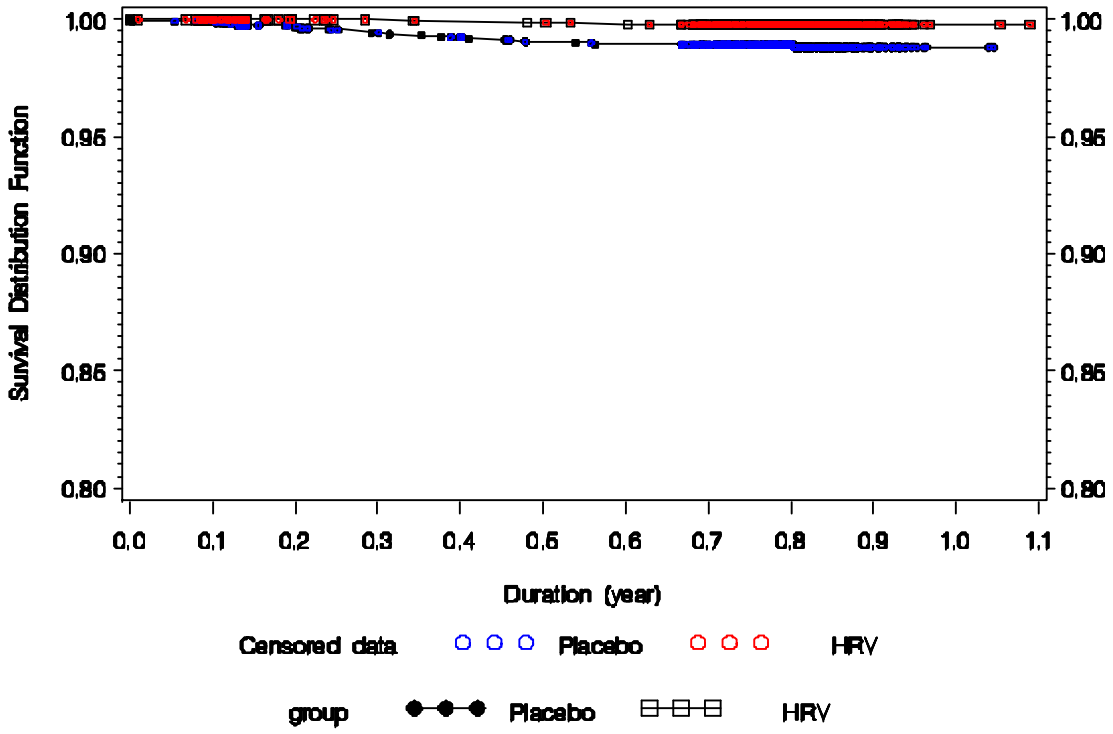

X Axis is cut at 11
Y Axis is cut at 0
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 36 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 6 (Total vaccinated cohort)**



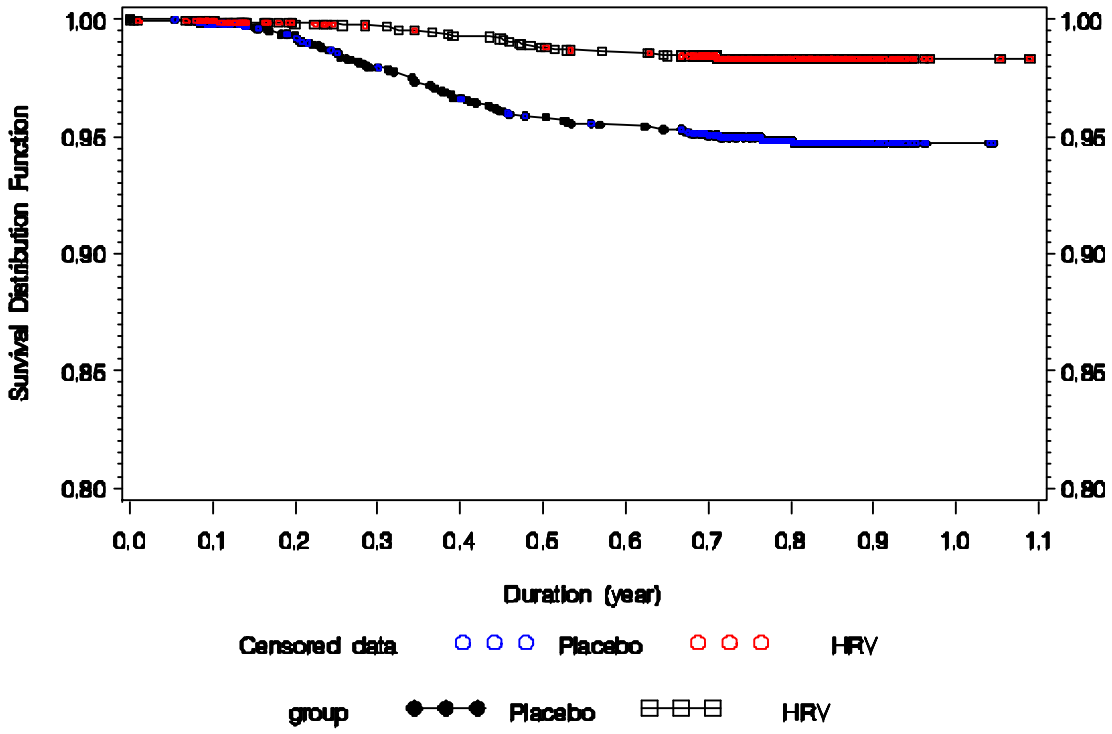

Y Axis is cut at 0.8

**Figure 37 The Kaplan Meier curve for any RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)**



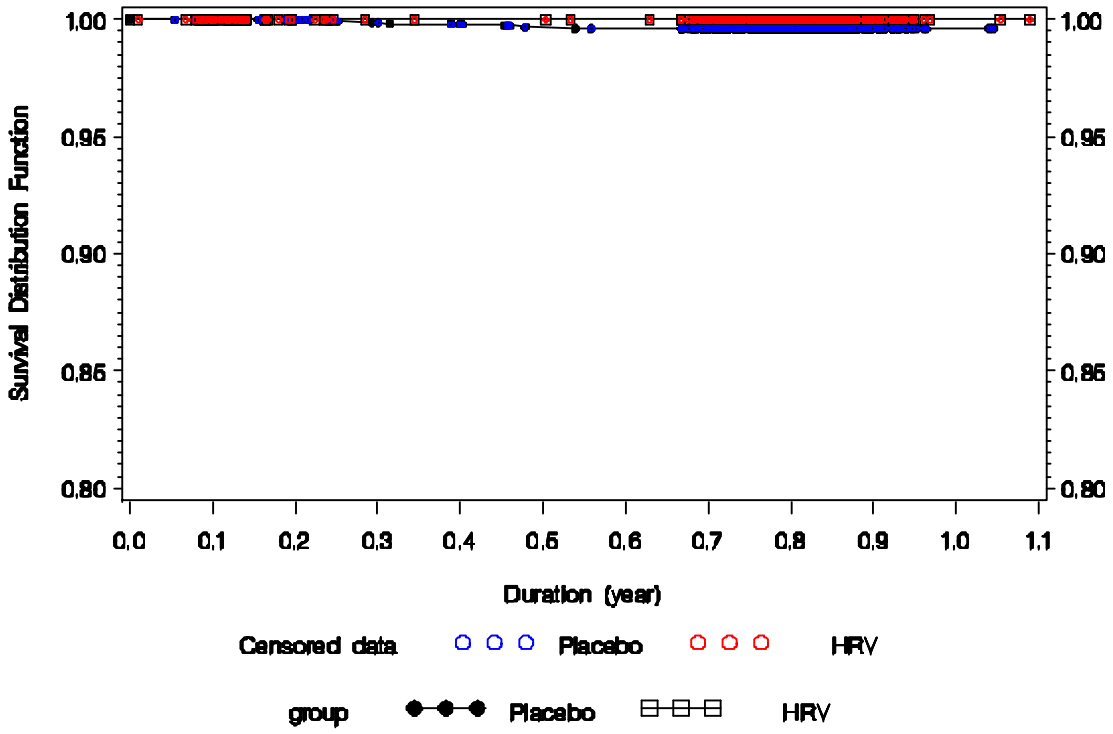

Y Axis is cut at 0.8

**Figure 38 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 6 (Total vaccinated cohort)**



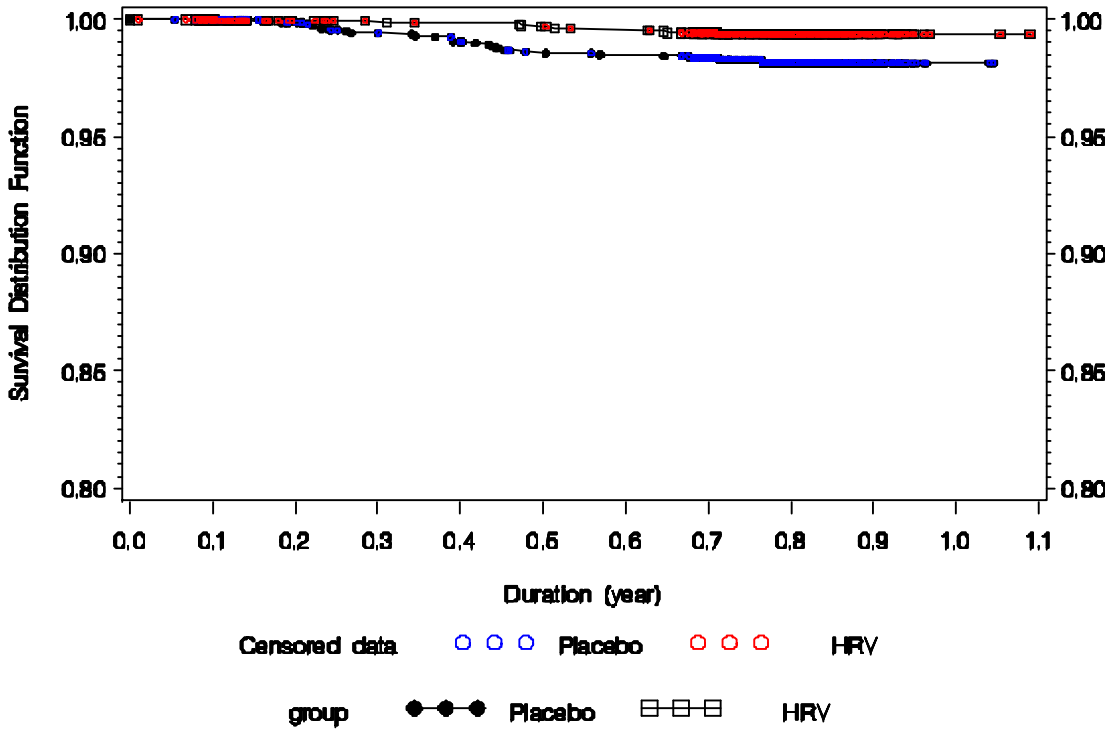

Y Axis is cut at 0.8

**Figure 39 The Kaplan Meier curve for severe RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)**




Y Axis is cut at 0.8

**Figure 40** **The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from Dose 1 up to Visit 6 (Total vaccinated cohort)**




Y Axis is cut at 0.8

## 11.5.5. Characterization of GE episodes from Dose 1 up to before Dose 2

**Table 171** **Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 1515 | 90.9 | 1507 | 90.4 | 3022 | 90.7 |
| | 1 | 140 | 8.4 | 154 | 9.2 | 294 | 8.8 |
| | 2 | 10 | 0.6 | 5 | 0.3 | 15 | 0.5 |
| | 3 | 1 | 0.1 | 1 | 0.1 | 2 | 0.1 |
| | Any | 151 | 9.1 | 160 | 9.6 | 311 | 9.3 |
| RVGE | 0 | 1665 | 99.9 | 1665 | 99.9 | 3330 | 99.9 |
| | 1 | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| | Any | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| Severe GE | 0 | 1652 | 99.2 | 1643 | 98.6 | 3295 | 98.9 |
| | 1 | 14 | 0.8 | 24 | 1.4 | 38 | 1.1 |
| | Any | 14 | 0.8 | 24 | 1.4 | 38 | 1.1 |
| Severe RVGE | 0 | 1666 | 100 | 1667 | 100 | 3333 | 100 |
| | Any | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 172 Number of GE episodes reported Dose 1 up to before Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 99 | 60.7 | 100 | 59.9 |
| | Moderate (7-10) | 41 | 25.2 | 38 | 22.8 |
| | Severe (≥11) | 14 | 8.6 | 24 | 14.4 |
| | Unknown | 9 | 5.5 | 5 | 3.0 |
| | Any | 154 | 94.5 | 162 | 97.0 |
| RVGE | Mild (1-6) | 1 | 100 | 1 | 50.0 |
| | Moderate (7-10) | 0 | 0.0 | 1 | 50.0 |
| | Any | 1 | 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

## Table 173 Percentage of GE episodes with no available stool results Dose 1 up to before Dose 2 (Total vaccinated cohort)

| | HRV N' = 163 | | Placebo N' = 167 | | Total N' = 330 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 75 | 46.0 | 63 | 37.7 | 138 | 41.8 |
| no stools collected | 75 | 46.0 | 63 | 37.7 | 138 | 41.8 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 174 Percentage of subjects with RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| Characteristics | n | % | n | % |
| Any | 1 | 0.1 | 2 | 0.1 |
| G1 WT | 0 | 0.0 | 1 | 0.1 |
| G2 | 1 | 0.1 | 1 | 0.1 |
| P4 | 1 | 0.1 | 1 | 0.1 |
| P8 WT | 0 | 0.0 | 1 | 0.1 |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one RV GE episode whatever the serotype
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 175 Percentage of subjects with severe RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

No record exists

## Table 176 Number of RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=1 | | Placebo N'=2 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+P8WT | 0 | 0.00 | 1 | 50.00 |
| G2+P4 | 1 | 100.0 | 1 | 50.00 |

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 to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 177 Number of severe RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

No record exists for this table

## Table 178 Duration (in years) of efficacy follow-up period - Dose 1 up to before Dose 2 (Total vaccinated cohort)

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| Characteristics | Parameters | Value | Value |
| Duration in years | Sum | 148.8 | 148.8 |
| | Mean | 0.09 | 0.09 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 0.08 | 0.08 |
| | Median | 0.08 | 0.08 |
| | Q3 | 0.09 | 0.09 |
| | Maximum | 0.79 | 0.76 |

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

## 11.5.6. Vaccine efficacy during the period from Dose 1 before Dose 2

### 11.5.6.1. Vaccine efficacy against severe RV GE

**Table 179 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

No record exists for this table

### 11.5.6.2. Vaccine efficacy against any RV GE

**Table 180 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 50.0 | -861.0 | 99.2 | 1.000 |
| Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |

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

### 11.5.6.3. Vaccine efficacy against hospitalisation due to RV

**Table 181 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

No record exists for this table

### 11.5.6.4. Vaccine efficacy against all cause GE

**Table 182 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 151 | 9.1 | 7.7 | 10.5 | 5.6 | -18.7 | 24.9 | 0.654 |
| Placebo | 1667 | 160 | 9.6 | 8.2 | 11.1 | - | - | - | - |

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

**Table 183 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 14 | 0.8 | 0.5 | 1.4 | 41.6 | -17.5 | 72.1 | 0.144 |
| Placebo | 1667 | 24 | 1.4 | 0.9 | 2.1 | - | - | - | - |

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

## 11.5.7. Characterization of GE episodes from Dose 1 up to 2 weeks post dose 2

**Table 184 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort )**

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| Characteristics | Number of episodes | n | % | n | % | n | % |
| GE | 0 | 1450 | 87.0 | 1450 | 87.0 | 2900 | 87.0 |
| | 1 | 190 | 11.4 | 196 | 11.8 | 386 | 11.6 |
| | 2 | 22 | 1.3 | 18 | 1.1 | 40 | 1.2 |
| | 3 | 4 | 0.2 | 2 | 0.1 | 6 | 0.2 |
| | 4 | 0 | 0.0 | 1 | 0.1 | 1 | 0.0 |
| | Any | 216 | 13.0 | 217 | 13.0 | 433 | 13.0 |
| RVGE | 0 | 1664 | 99.9 | 1661 | 99.6 | 3325 | 99.8 |
| | 1 | 2 | 0.1 | 6 | 0.4 | 8 | 0.2 |
| | Any | 2 | 0.1 | 6 | 0.4 | 8 | 0.2 |
| Severe GE | 0 | 1646 | 98.8 | 1635 | 98.1 | 3281 | 98.4 |
| | 1 | 20 | 1.2 | 32 | 1.9 | 52 | 1.6 |
| | Any | 20 | 1.2 | 32 | 1.9 | 52 | 1.6 |
| Severe RVGE | 0 | 1665 | 99.9 | 1667 | 100 | 3332 | 100 |
| | 1 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |

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

## Table 185 Number of GE episodes reported from Dose 1 up to 2 weeks post-Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 156 | 63.4 | 146 | 60.3 |
| | Moderate (7-10) | 61 | 24.8 | 58 | 24.0 |
| | Severe (≥11) | 20 | 8.1 | 32 | 13.2 |
| | Unknown | 9 | 3.7 | 6 | 2.5 |
| | Any | 237 | 96.3 | 236 | 97.5 |
| RVGE | Mild (1-6) | 1 | 50.0 | 2 | 33.3 |
| | Moderate (7-10) | 0 | 0.0 | 4 | 66.7 |
| | Severe (≥11) | 1 | 50.0 | 0 | 0.0 |
| | Any | 2 | 100 | 6 | 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

## Table 186 Percentage of GE episodes with no available stool results from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

| | HRV N' = 246 | | Placebo N' = 242 | | Total N' = 488 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 115 | 46.7 | 97 | 40.1 | 212 | 43.4 |
| no stools collected | 115 | 46.7 | 97 | 40.1 | 212 | 43.4 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 187 Percentage of subjects with RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| Characteristics | n | % | n | % |
| Any | 2 | 0.1 | 6 | 0.4 |
| G1 wild type | 0 | 0.0 | 3 | 0.2 |
| G2 | 2 | 0.1 | 3 | 0.2 |
| P4 | 2 | 0.1 | 4 | 0.2 |
| P8 wild type | 0 | 0.0 | 2 | 0.1 |

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

## Table 188 Percentage of subjects with severe RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** |
| Any | 1 | 0.1 | 0 | 0.0 |
| G2 | 1 | 0.1 | 0 | 0.0 |
| P4 | 1 | 0.1 | 0 | 0.0 |

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 severe RV GE episode whatever the serotype

## Table 189 Number of RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=2 | | Placebo N'=6 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+P4 | 0 | 0.00 | 1 | 16.67 |
| G1WT+P8WT | 0 | 0.00 | 2 | 33.33 |
| G2+P4 | 2 | 100.0 | 3 | 50.00 |

WT=Wild Type
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 up to 2 weeks post dose 2

## Table 190 Number of severe RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=1 | | Placebo N'=0 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G2+P4 | 1 | 100.0 | 0 | 0.00 |

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 severe RV GE episodes reported from dose 1 up to 2 weeks post dose 2

## Table 191 Duration (in years) of efficacy follow-up period from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 210.1 | 210.0 |
| | Mean | 0.13 | 0.13 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 0.12 | 0.12 |
| | Median | 0.12 | 0.12 |
| | Q3 | 0.13 | 0.13 |
| | Maximum | 0.79 | 0.76 |

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

## 11.5.8. Vaccine efficacy during the period from Dose 1 up to 2 weeks post dose 2

### 11.5.8.1. Vaccine efficacy against severe RV GE

**Table 192 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | Und. | Und. | Und. | 1.000 |
| Placebo | 1667 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Und = Can not be estimated

### 11.5.8.2. Vaccine efficacy against any RV GE

**Table 193 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 66.6 | -86.5 | 96.7 | 0.289 |
| Placebo | 1667 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |

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

### 11.5.8.3. Vaccine efficacy against hospitalisation due to RV

**Table 194 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

No record exists for this table

### 11.5.8.4. Vaccine efficacy against all cause GE

**Table 195 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 216 | 13.0 | 11.4 | 14.7 | 0.4 | -20.8 | 17.9 | 1.000 |
| Placebo | 1667 | 217 | 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
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 196 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 20 | 1.2 | 0.7 | 1.8 | 37.5 | -12.7 | 66.1 | 0.127 |
| Placebo | 1667 | 32 | 1.9 | 1.3 | 2.7 | - | - | - | - |

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

## 11.6. Safety Results

### 11.6.1. Total vaccinated cohort analysis

**Table 197 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort)**

| | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|
| Total number of doses received | n | % | n | % | n | % |
| 1 | 67 | 4.0 | 70 | 4.2 | 137 | 4.1 |
| 2 | 1599 | 96.0 | 1597 | 95.8 | 3196 | 95.9 |
| Any | 1666 | 100 | 1667 | 100 | 3333 | 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

## Table 198 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort- except immunogenicity sub-cohorts)

| | HRV N = 1513 | | Placebo N = 1514 | | Total N = 3027 | |
|---|---|---|---|---|---|---|
| Total number of doses received | n | % | n | % | n | % |
| 1 | 64 | 4.2 | 68 | 4.5 | 132 | 4.4 |
| 2 | 1449 | 95.8 | 1446 | 95.5 | 2895 | 95.6 |
| Any | 1513 | 100 | 1514 | 100 | 3027 | 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

## Table 199 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | HRV DTPA VACCINE N = 153 | | HRV OPV N = 153 | | HRV ROTARIX N = 153 | | Placebo DTPA VACCINE N = 153 | | Placebo OPV N = 153 | | Placebo PLACEBO N = 153 | | Total DTPA VACCINE N = 306 | | Total OPV N = 306 | | Total PLACEBO N = 306 | | Total ROTARIX N = 306 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total number of doses received | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| 0 | 3 | 2.0 | 0 | 0.0 | 0 | 0.0 | 2 | 1.3 | 0 | 0.0 | 0 | 0.0 | 5 | 1.6 | 0 | 0.0 | 153 | 50.0 | 153 | 50.0 |
| 1 | 1 | 0.7 | 3 | 2.0 | 3 | 2.0 | 1 | 0.7 | 2 | 1.3 | 2 | 1.3 | 2 | 0.7 | 5 | 1.6 | 2 | 0.7 | 3 | 1.0 |
| 2 | 1 | 0.7 | 1 | 0.7 | 150 | 98.0 | 2 | 1.3 | 1 | 0.7 | 151 | 98.7 | 3 | 1.0 | 2 | 0.7 | 151 | 49.3 | 150 | 49.0 |
| 3 | 148 | 96.7 | 149 | 97.4 | 0 | 0.0 | 148 | 96.7 | 150 | 98.0 | 0 | 0.0 | 296 | 96.7 | 299 | 97.7 | 0 | 0.0 | 0 | 0.0 |
| Any | 150 | 98.0 | 153 | 100 | 153 | 100 | 151 | 98.7 | 153 | 100 | 153 | 100 | 301 | 98.4 | 306 | 100 | 153 | 50.0 | 153 | 50.0 |

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

## Table 200 Compliance in returning symptom sheets (Total vaccinated cohort- except immunogenicity sub cohort 2)

| Dose | Group | Number of doses | Doses NOT according to protocol | Number of general SS | Compliance % general SS |
|---|---|---|---|---|---|
| 1 | HRV | 1513 | 0 | 1485 | 98.1 |
| | Placebo | 1514 | 0 | 1483 | 98.0 |
| 2 | HRV | 1449 | 1 | 1448 | 99.9 |
| | Placebo | 1446 | 0 | 1446 | 100 |

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

**Table 201 Compliance in returning symptom sheets (Total vaccinated cohort- Immunogenicity sub cohort 2)**

| Dose | Group | Number of doses | Doses NOT according to protocol | Number of general SS | Compliance % general SS | Number of local SS | Compliance % local SS |
|---|---|---|---|---|---|---|---|
| 1 | HRV | 153 | 0 | 150 | 98.0 | 0 | 0.0 |
| | Placebo | 153 | 0 | 151 | 98.7 | 0 | 0.0 |
| 2 | HRV | 150 | 0 | 149 | 99.3 | 149 | 99.3 |
| | Placebo | 151 | 0 | 150 | 99.3 | 150 | 99.3 |

SS = Symptom sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100
*Local symptom sheet for 1st dose of DTPa which is co-administered with 2nd dose of HRV / Placebo

## 11.6.1.1. Overall incidence of adverse events

**Table 202 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0 - 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 496 | 32.8 | 30.4 | 35.2 |
| | Placebo | 1514 | 562 | 37.1 | 34.7 | 39.6 |
| Dose 2 | HRV | 1449 | 386 | 26.6 | 24.4 | 29.0 |
| | Placebo | 1446 | 389 | 26.9 | 24.6 | 29.3 |
| Overall/dose | HRV | 2962 | 882 | 29.8 | 28.1 | 31.5 |
| | Placebo | 2960 | 951 | 32.1 | 30.4 | 33.8 |
| Overall/subject | HRV | 1513 | 669 | 44.2 | 41.7 | 46.8 |
| | Placebo | 1514 | 716 | 47.3 | 44.8 | 49.8 |

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

## Table 203 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 589 | 38.9 | 36.5 | 41.4 |
| | Placebo | 1514 | 645 | 42.6 | 40.1 | 45.1 |
| Dose 2 | HRV | 1449 | 448 | 30.9 | 28.5 | 33.4 |
| | Placebo | 1446 | 448 | 31.0 | 28.6 | 33.4 |
| Overall/dose | HRV | 2962 | 1037 | 35.0 | 33.3 | 36.8 |
| | Placebo | 2960 | 1093 | 36.9 | 35.2 | 38.7 |
| Overall/subject | HRV | 1513 | 779 | 51.5 | 48.9 | 54.0 |
| | Placebo | 1514 | 814 | 53.8 | 51.2 | 56.3 |

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

## Table 204 Percentage of doses and of subjects reporting incidence of Grade 3 AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 113 | 7.5 | 6.2 | 8.9 |
| | Placebo | 1514 | 109 | 7.2 | 5.9 | 8.6 |
| Dose 2 | HRV | 1449 | 74 | 5.1 | 4.0 | 6.4 |
| | Placebo | 1446 | 62 | 4.3 | 3.3 | 5.5 |
| Overall/dose | HRV | 2962 | 187 | 6.3 | 5.5 | 7.3 |
| | Placebo | 2960 | 171 | 5.8 | 5.0 | 6.7 |
| Overall/subject | HRV | 1513 | 170 | 11.2 | 9.7 | 12.9 |
| | Placebo | 1514 | 153 | 10.1 | 8.6 | 11.7 |

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

## Table 205 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) that are causally related to the vaccination reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 169 | 11.2 | 9.6 | 12.9 |
| | Placebo | 1514 | 150 | 9.9 | 8.4 | 11.5 |
| Dose 2 | HRV | 1449 | 113 | 7.8 | 6.5 | 9.3 |
| | Placebo | 1446 | 102 | 7.1 | 5.8 | 8.5 |
| Overall/dose | HRV | 2962 | 282 | 9.5 | 8.5 | 10.6 |
| | Placebo | 2960 | 252 | 8.5 | 7.5 | 9.6 |
| Overall/subject | HRV | 1513 | 239 | 15.8 | 14.0 | 17.7 |
| | Placebo | 1514 | 222 | 14.7 | 12.9 | 16.5 |

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

## Table 206 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) that are causally related to the vaccination reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 204 | 13.5 | 11.8 | 15.3 |
| | Placebo | 1514 | 172 | 11.4 | 9.8 | 13.1 |
| Dose 2 | HRV | 1449 | 135 | 9.3 | 7.9 | 10.9 |
| | Placebo | 1446 | 125 | 8.6 | 7.2 | 10.2 |
| Overall/dose | HRV | 2962 | 339 | 11.4 | 10.3 | 12.6 |
| | Placebo | 2960 | 297 | 10.0 | 9.0 | 11.2 |
| Overall/subject | HRV | 1513 | 292 | 19.3 | 17.3 | 21.4 |
| | Placebo | 1514 | 259 | 17.1 | 15.2 | 19.1 |

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

## Table 207 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 65 | 42.5 | 34.5 | 50.7 | 153 | 65 | 42.5 | 34.5 | 50.7 | - | - | - | - | - |
| | Placebo | 153 | 59 | 38.6 | 30.8 | 46.8 | 153 | 59 | 38.6 | 30.8 | 46.8 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 55 | 36.7 | 29.0 | 44.9 | 150 | 45 | 30.0 | 22.8 | 38.0 | 150 | 24 | 16.0 | 10.5 | 22.9 |
| | Placebo | 151 | 55 | 36.4 | 28.8 | 44.6 | 151 | 44 | 29.1 | 22.0 | 37.1 | 151 | 18 | 11.9 | 7.2 | 18.2 |
| Overall/dose | HRV | 303 | 120 | 39.6 | 34.1 | 45.4 | 303 | 110 | 36.3 | 30.9 | 42.0 | - | - | - | - | - |
| | Placebo | 304 | 114 | 37.5 | 32.0 | 43.2 | 304 | 103 | 33.9 | 28.6 | 39.5 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 88 | 57.5 | 49.3 | 65.5 | 153 | 81 | 52.9 | 44.7 | 61.1 | - | - | - | - | - |
| | Placebo | 153 | 81 | 52.9 | 44.7 | 61.1 | 153 | 77 | 50.3 | 42.1 | 58.5 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by GSK scale Fever

## Table 208 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 67 | 43.8 | 35.8 | 52.0 | 153 | 67 | 43.8 | 35.8 | 52.0 | - | - | - | - | - |
| | Placebo | 153 | 61 | 39.9 | 32.1 | 48.1 | 153 | 61 | 39.9 | 32.1 | 48.1 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 57 | 38.0 | 30.2 | 46.3 | 150 | 47 | 31.3 | 24.0 | 39.4 | 150 | 24 | 16.0 | 10.5 | 22.9 |
| | Placebo | 151 | 59 | 39.1 | 31.2 | 47.3 | 151 | 49 | 32.5 | 25.1 | 40.5 | 151 | 18 | 11.9 | 7.2 | 18.2 |
| Overall/dose | HRV | 303 | 124 | 40.9 | 35.3 | 46.7 | 303 | 114 | 37.6 | 32.1 | 43.3 | - | - | - | - | - |
| | Placebo | 304 | 120 | 39.5 | 33.9 | 45.2 | 304 | 110 | 36.2 | 30.8 | 41.9 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 92 | 60.1 | 51.9 | 67.9 | 153 | 85 | 55.6 | 47.3 | 63.6 | - | - | - | - | - |
| | Placebo | 153 | 85 | 55.6 | 47.3 | 63.6 | 153 | 81 | 52.9 | 44.7 | 61.1 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by Chinese scale Fever

## Table 209 Percentage of doses and of subjects reporting incidence of Grade 3 AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 3 | 2.0 | 0.4 | 5.6 | - | - | - | - | - |
| | Placebo | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 6 | 3.9 | 1.5 | 8.3 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 6 | 4.0 | 1.5 | 8.5 | 150 | 5 | 3.3 | 1.1 | 7.6 | 150 | 2 | 1.3 | 0.2 | 4.7 |
| | Placebo | 151 | 2 | 1.3 | 0.2 | 4.7 | 151 | 1 | 0.7 | 0.0 | 3.6 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| Overall/dose | HRV | 303 | 9 | 3.0 | 1.4 | 5.6 | 303 | 8 | 2.6 | 1.1 | 5.1 | - | - | - | - | - |
| | Placebo | 304 | 8 | 2.6 | 1.1 | 5.1 | 304 | 7 | 2.3 | 0.9 | 4.7 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 8 | 5.2 | 2.3 | 10.0 | 153 | 7 | 4.6 | 1.9 | 9.2 | - | - | - | - | - |
| | Placebo | 153 | 7 | 4.6 | 1.9 | 9.2 | 153 | 6 | 3.9 | 1.5 | 8.3 | - | - | - | - | - |

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

## Table 210 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) assessed as grade 3 and are causally related to the vaccination reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 3 | 2.0 | 0.4 | 5.6 | - | - | - | - | - |
| | Placebo | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 4 | 2.7 | 0.7 | 6.7 | 150 | 2 | 1.3 | 0.2 | 4.7 | 150 | 2 | 1.3 | 0.2 | 4.7 |
| | Placebo | 151 | 2 | 1.3 | 0.2 | 4.7 | 151 | 1 | 0.7 | 0.0 | 3.6 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| Overall/dose | HRV | 303 | 7 | 2.3 | 0.9 | 4.7 | 303 | 5 | 1.7 | 0.5 | 3.8 | - | - | - | - | - |
| | Placebo | 304 | 4 | 1.3 | 0.4 | 3.3 | 304 | 3 | 1.0 | 0.2 | 2.9 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 4 | 2.6 | 0.7 | 6.6 | - | - | - | - | - |
| | Placebo | 153 | 4 | 2.6 | 0.7 | 6.6 | 153 | 3 | 2.0 | 0.4 | 5.6 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)

**Table 211 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) requiring medical attention reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 13 | 8.5 | 4.6 | 14.1 | 153 | 13 | 8.5 | 4.6 | 14.1 | - | - | - | - | - |
| | Placebo | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 12 | 7.8 | 4.1 | 13.3 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 1 | 0.7 | 0.0 | 3.7 |
| | Placebo | 151 | 5 | 3.3 | 1.1 | 7.6 | 151 | 5 | 3.3 | 1.1 | 7.6 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Overall/dose | HRV | 303 | 21 | 6.9 | 4.3 | 10.4 | 303 | 21 | 6.9 | 4.3 | 10.4 | - | - | - | - | - |
| | Placebo | 304 | 17 | 5.6 | 3.3 | 8.8 | 304 | 17 | 5.6 | 3.3 | 8.8 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 19 | 12.4 | 7.6 | 18.7 | 153 | 19 | 12.4 | 7.6 | 18.7 | - | - | - | - | - |
| | Placebo | 153 | 17 | 11.1 | 6.6 | 17.2 | 153 | 17 | 11.1 | 6.6 | 17.2 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by GSK scale Fever

**Table 212 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) requiring medical attention reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 14 | 9.2 | 5.1 | 14.9 | 153 | 14 | 9.2 | 5.1 | 14.9 | - | - | - | - | - |
| | Placebo | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 12 | 7.8 | 4.1 | 13.3 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 1 | 0.7 | 0.0 | 3.7 |
| | Placebo | 151 | 6 | 4.0 | 1.5 | 8.4 | 151 | 6 | 4.0 | 1.5 | 8.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Overall/dose | HRV | 303 | 22 | 7.3 | 4.6 | 10.8 | 303 | 22 | 7.3 | 4.6 | 10.8 | - | - | - | - | - |
| | Placebo | 304 | 18 | 5.9 | 3.5 | 9.2 | 304 | 18 | 5.9 | 3.5 | 9.2 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 20 | 13.1 | 8.2 | 19.5 | 153 | 20 | 13.1 | 8.2 | 19.5 | - | - | - | - | - |
| | Placebo | 153 | 18 | 11.8 | 7.1 | 18.0 | 153 | 18 | 11.8 | 7.1 | 18.0 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom at the study vaccine site
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom at the study vaccine site
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by Chinese scale Fever

### 11.6.1.2. Solicited local adverse events

**Table 213 Percentage of subjects reporting each solicited local symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 2 | | | | | | | | | | | |
| Pain | All | 150 | 14 | 9.3 | 5.2 | 15.2 | 151 | 9 | 6.0 | 2.8 | 11.0 |
| | Grade 3 | 150 | 2 | 1.3 | 0.2 | 4.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Redness (mm) | All | 150 | 20 | 13.3 | 8.3 | 19.8 | 151 | 13 | 8.6 | 4.7 | 14.3 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Swelling (mm) | All | 150 | 13 | 8.7 | 4.7 | 14.4 | 151 | 6 | 4.0 | 1.5 | 8.4 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |

For each dose:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Dose 2 of HRV/placebo= Dose 1 of DTPa

### 11.6.1.3. Solicited general adverse events

**Table 214 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Irritability/Fussiness | All | 1666 | 369 | 22.1 | 20.2 | 24.2 | 1667 | 397 | 23.8 | 21.8 | 25.9 |
| | Grade 3 | 1666 | 28 | 1.7 | 1.1 | 2.4 | 1667 | 30 | 1.8 | 1.2 | 2.6 |
| | Related | 1666 | 128 | 7.7 | 6.4 | 9.1 | 1667 | 107 | 6.4 | 5.3 | 7.7 |
| | Grade 3 Related | 1666 | 13 | 0.8 | 0.4 | 1.3 | 1667 | 12 | 0.7 | 0.4 | 1.3 |
| Loss of appetite | All | 1666 | 209 | 12.5 | 11.0 | 14.2 | 1667 | 209 | 12.5 | 11.0 | 14.2 |
| | Grade 3 | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 5 | 0.3 | 0.1 | 0.7 |
| | Related | 1666 | 76 | 4.6 | 3.6 | 5.7 | 1667 | 60 | 3.6 | 2.8 | 4.6 |
| | Grade 3 Related | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1666 | 211 | 12.7 | 11.1 | 14.4 | 1667 | 223 | 13.4 | 11.8 | 15.1 |
| | Grade 3 | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| | Related | 1666 | 74 | 4.4 | 3.5 | 5.5 | 1667 | 59 | 3.5 | 2.7 | 4.5 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1666 | 44 | 2.6 | 1.9 | 3.5 | 1667 | 68 | 4.1 | 3.2 | 5.1 |
| | Grade 3 | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| | Related | 1666 | 19 | 1.1 | 0.7 | 1.8 | 1667 | 16 | 1.0 | 0.5 | 1.6 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| **Dose 2** | | | | | | | | | | | |
| Irritability/Fussiness | All | 1599 | 215 | 13.4 | 11.8 | 15.2 | 1597 | 233 | 14.6 | 12.9 | 16.4 |
| | Grade 3 | 1599 | 23 | 1.4 | 0.9 | 2.2 | 1597 | 18 | 1.1 | 0.7 | 1.8 |
| | Related | 1599 | 81 | 5.1 | 4.0 | 6.3 | 1597 | 66 | 4.1 | 3.2 | 5.2 |
| | Grade 3 Related | 1599 | 10 | 0.6 | 0.3 | 1.1 | 1597 | 9 | 0.6 | 0.3 | 1.1 |
| Loss of appetite | All | 1599 | 139 | 8.7 | 7.4 | 10.2 | 1597 | 133 | 8.3 | 7.0 | 9.8 |
| | Grade 3 | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 4 | 0.3 | 0.1 | 0.6 |
| | Related | 1599 | 48 | 3.0 | 2.2 | 4.0 | 1597 | 39 | 2.4 | 1.7 | 3.3 |
| | Grade 3 Related | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 3 | 0.2 | 0.0 | 0.5 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1599 | 152 | 9.5 | 8.1 | 11.1 | 1597 | 151 | 9.5 | 8.1 | 11.0 |
| | Grade 3 | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| | Related | 1599 | 42 | 2.6 | 1.9 | 3.5 | 1597 | 40 | 2.5 | 1.8 | 3.4 |
| | Grade 3 Related | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1599 | 49 | 3.1 | 2.3 | 4.0 | 1597 | 47 | 2.9 | 2.2 | 3.9 |
| | Grade 3 | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| | Related | 1599 | 8 | 0.5 | 0.2 | 1.0 | 1597 | 11 | 0.7 | 0.3 | 1.2 |
| | Grade 3 Related | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 1 | 0.1 | 0.0 | 0.3 |

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

**Table 215 Percentage of doses and subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Overall/dose** | | | | | | | | | | | |
| Irritability/Fussiness | All | 3265 | 584 | 17.9 | 16.6 | 19.2 | 3264 | 630 | 19.3 | 18.0 | 20.7 |
| | Grade 3 | 3265 | 51 | 1.6 | 1.2 | 2.0 | 3264 | 48 | 1.5 | 1.1 | 1.9 |
| | Related | 3265 | 209 | 6.4 | 5.6 | 7.3 | 3264 | 173 | 5.3 | 4.6 | 6.1 |
| | Grade 3 Related | 3265 | 23 | 0.7 | 0.4 | 1.1 | 3264 | 21 | 0.6 | 0.4 | 1.0 |
| Loss of appetite | All | 3265 | 348 | 10.7 | 9.6 | 11.8 | 3264 | 342 | 10.5 | 9.4 | 11.6 |
| | Grade 3 | 3265 | 5 | 0.2 | 0.0 | 0.4 | 3264 | 9 | 0.3 | 0.1 | 0.5 |
| | Related | 3265 | 124 | 3.8 | 3.2 | 4.5 | 3264 | 99 | 3.0 | 2.5 | 3.7 |
| | Grade 3 Related | 3265 | 4 | 0.1 | 0.0 | 0.3 | 3264 | 5 | 0.2 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 3265 | 363 | 11.1 | 10.1 | 12.2 | 3264 | 374 | 11.5 | 10.4 | 12.6 |
| | Grade 3 | 3265 | 1 | 0.0 | 0.0 | 0.2 | 3264 | 3 | 0.1 | 0.0 | 0.3 |
| | Related | 3265 | 116 | 3.6 | 2.9 | 4.2 | 3264 | 99 | 3.0 | 2.5 | 3.7 |
| | Grade 3 Related | 3265 | 0 | 0.0 | 0.0 | 0.1 | 3264 | 1 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 3265 | 93 | 2.8 | 2.3 | 3.5 | 3264 | 115 | 3.5 | 2.9 | 4.2 |
| | Grade 3 | 3265 | 1 | 0.0 | 0.0 | 0.2 | 3264 | 3 | 0.1 | 0.0 | 0.3 |
| | Related | 3265 | 27 | 0.8 | 0.5 | 1.2 | 3264 | 27 | 0.8 | 0.5 | 1.2 |
| | Grade 3 Related | 3265 | 0 | 0.0 | 0.0 | 0.1 | 3264 | 1 | 0.0 | 0.0 | 0.2 |
| **Overall/subject** | | | | | | | | | | | |
| Irritability/Fussiness | All | 1666 | 471 | 28.3 | 26.1 | 30.5 | 1667 | 500 | 30.0 | 27.8 | 32.3 |
| | Grade 3 | 1666 | 48 | 2.9 | 2.1 | 3.8 | 1667 | 43 | 2.6 | 1.9 | 3.5 |
| | Related | 1666 | 176 | 10.6 | 9.1 | 12.1 | 1667 | 154 | 9.2 | 7.9 | 10.7 |
| | Grade 3 Related | 1666 | 20 | 1.2 | 0.7 | 1.8 | 1667 | 20 | 1.2 | 0.7 | 1.8 |
| Loss of appetite | All | 1666 | 296 | 17.8 | 16.0 | 19.7 | 1667 | 282 | 16.9 | 15.1 | 18.8 |
| | Grade 3 | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 9 | 0.5 | 0.2 | 1.0 |
| | Related | 1666 | 107 | 6.4 | 5.3 | 7.7 | 1667 | 90 | 5.4 | 4.4 | 6.6 |
| | Grade 3 Related | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 5 | 0.3 | 0.1 | 0.7 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1666 | 320 | 19.2 | 17.3 | 21.2 | 1667 | 333 | 20.0 | 18.1 | 22.0 |
| | Grade 3 | 1666 | 1 | 0.1 | 0.0 | 0.3 | 1667 | 3 | 0.2 | 0.0 | 0.5 |
| | Related | 1666 | 112 | 6.7 | 5.6 | 8.0 | 1667 | 96 | 5.8 | 4.7 | 7.0 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 1 | 0.1 | 0.0 | 0.3 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1666 | 89 | 5.3 | 4.3 | 6.5 | 1667 | 111 | 6.7 | 5.5 | 8.0 |
| | Grade 3 | 1666 | 1 | 0.1 | 0.0 | 0.3 | 1667 | 3 | 0.2 | 0.0 | 0.5 |
| | Related | 1666 | 27 | 1.6 | 1.1 | 2.3 | 1667 | 27 | 1.6 | 1.1 | 2.3 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 1 | 0.1 | 0.0 | 0.3 |

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

## Table 216 Percentage of subjects reporting fever during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 1666 | 211 | 12.7 | 11.1 | 14.4 | 1667 | 223 | 13.4 | 11.8 | 15.1 |
| | >37.0°C | 1666 | 211 | 12.7 | 11.1 | 14.4 | 1667 | 223 | 13.4 | 11.8 | 15.1 |
| | >37.5°C | 1666 | 32 | 1.9 | 1.3 | 2.7 | 1667 | 52 | 3.1 | 2.3 | 4.1 |
| | >38.0°C | 1666 | 11 | 0.7 | 0.3 | 1.2 | 1667 | 21 | 1.3 | 0.8 | 1.9 |
| | >38.5°C | 1666 | 6 | 0.4 | 0.1 | 0.8 | 1667 | 10 | 0.6 | 0.3 | 1.1 |
| | >39.0°C | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| **Dose 2** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 1599 | 152 | 9.5 | 8.1 | 11.1 | 1597 | 151 | 9.5 | 8.1 | 11.0 |
| | >37.0°C | 1599 | 152 | 9.5 | 8.1 | 11.1 | 1597 | 151 | 9.5 | 8.1 | 11.0 |
| | >37.5°C | 1599 | 40 | 2.5 | 1.8 | 3.4 | 1597 | 35 | 2.2 | 1.5 | 3.0 |
| | >38.0°C | 1599 | 17 | 1.1 | 0.6 | 1.7 | 1597 | 14 | 0.9 | 0.5 | 1.5 |
| | >38.5°C | 1599 | 5 | 0.3 | 0.1 | 0.7 | 1597 | 7 | 0.4 | 0.2 | 0.9 |
| | >39.0°C | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| **Overall/dose** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 3265 | 363 | 11.1 | 10.1 | 12.2 | 3264 | 374 | 11.5 | 10.4 | 12.6 |
| | >37.0°C | 3265 | 363 | 11.1 | 10.1 | 12.2 | 3264 | 374 | 11.5 | 10.4 | 12.6 |
| | >37.5°C | 3265 | 72 | 2.2 | 1.7 | 2.8 | 3264 | 87 | 2.7 | 2.1 | 3.3 |
| | >38.0°C | 3265 | 28 | 0.9 | 0.6 | 1.2 | 3264 | 35 | 1.1 | 0.7 | 1.5 |
| | >38.5°C | 3265 | 11 | 0.3 | 0.2 | 0.6 | 3264 | 17 | 0.5 | 0.3 | 0.8 |
| | >39.0°C | 3265 | 1 | 0.0 | 0.0 | 0.2 | 3264 | 3 | 0.1 | 0.0 | 0.3 |
| **Overall/subject** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 1666 | 320 | 19.2 | 17.3 | 21.2 | 1667 | 333 | 20.0 | 18.1 | 22.0 |
| | >37.0°C | 1666 | 320 | 19.2 | 17.3 | 21.2 | 1667 | 333 | 20.0 | 18.1 | 22.0 |
| | >37.5°C | 1666 | 71 | 4.3 | 3.3 | 5.3 | 1667 | 84 | 5.0 | 4.0 | 6.2 |
| | >38.0°C | 1666 | 28 | 1.7 | 1.1 | 2.4 | 1667 | 34 | 2.0 | 1.4 | 2.8 |
| | >38.5°C | 1666 | 11 | 0.7 | 0.3 | 1.2 | 1667 | 17 | 1.0 | 0.6 | 1.6 |
| | >39.0°C | 1666 | 1 | 0.1 | 0.0 | 0.3 | 1667 | 3 | 0.2 | 0.0 | 0.5 |

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

**Table 217 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Cough/runny nose | All | 1513 | 191 | 12.6 | 11.0 | 14.4 | 1514 | 221 | 14.6 | 12.9 | 16.5 |
| | Grade 3 | 1513 | 9 | 0.6 | 0.3 | 1.1 | 1514 | 4 | 0.3 | 0.1 | 0.7 |
| | Related | 1513 | 38 | 2.5 | 1.8 | 3.4 | 1514 | 30 | 2.0 | 1.3 | 2.8 |
| | Grade 3 Related | 1513 | 5 | 0.3 | 0.1 | 0.8 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Diarrhoea | All | 1513 | 80 | 5.3 | 4.2 | 6.5 | 1514 | 87 | 5.7 | 4.6 | 7.0 |
| | Grade 3 | 1513 | 31 | 2.0 | 1.4 | 2.9 | 1514 | 45 | 3.0 | 2.2 | 4.0 |
| | Related | 1513 | 38 | 2.5 | 1.8 | 3.4 | 1514 | 36 | 2.4 | 1.7 | 3.3 |
| | Grade 3 Related | 1513 | 17 | 1.1 | 0.7 | 1.8 | 1514 | 22 | 1.5 | 0.9 | 2.2 |
| Irritability/Fussiness | All | 1513 | 325 | 21.5 | 19.4 | 23.6 | 1514 | 357 | 23.6 | 21.5 | 25.8 |
| | Grade 3 | 1513 | 26 | 1.7 | 1.1 | 2.5 | 1514 | 26 | 1.7 | 1.1 | 2.5 |
| | Related | 1513 | 113 | 7.5 | 6.2 | 8.9 | 1514 | 102 | 6.7 | 5.5 | 8.1 |
| | Grade 3 Related | 1513 | 11 | 0.7 | 0.4 | 1.3 | 1514 | 11 | 0.7 | 0.4 | 1.3 |
| Loss of appetite | All | 1513 | 178 | 11.8 | 10.2 | 13.5 | 1514 | 186 | 12.3 | 10.7 | 14.0 |
| | Grade 3 | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 3 | 0.2 | 0.0 | 0.6 |
| | Related | 1513 | 63 | 4.2 | 3.2 | 5.3 | 1514 | 58 | 3.8 | 2.9 | 4.9 |
| | Grade 3 Related | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 2 | 0.1 | 0.0 | 0.5 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1513 | 199 | 13.2 | 11.5 | 15.0 | 1514 | 213 | 14.1 | 12.4 | 15.9 |
| | Grade 3 | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1513 | 66 | 4.4 | 3.4 | 5.5 | 1514 | 55 | 3.6 | 2.7 | 4.7 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1513 | 41 | 2.7 | 2.0 | 3.7 | 1514 | 66 | 4.4 | 3.4 | 5.5 |
| | Grade 3 | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1513 | 17 | 1.1 | 0.7 | 1.8 | 1514 | 15 | 1.0 | 0.6 | 1.6 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Vomiting | All | 1513 | 165 | 10.9 | 9.4 | 12.6 | 1514 | 176 | 11.6 | 10.1 | 13.3 |
| | Grade 3 | 1513 | 59 | 3.9 | 3.0 | 5.0 | 1514 | 56 | 3.7 | 2.8 | 4.8 |
| | Related | 1513 | 38 | 2.5 | 1.8 | 3.4 | 1514 | 26 | 1.7 | 1.1 | 2.5 |
| | Grade 3 Related | 1513 | 16 | 1.1 | 0.6 | 1.7 | 1514 | 13 | 0.9 | 0.5 | 1.5 |
| **Dose 2** | | | | | | | | | | | |
| Cough/runny nose | All | 1449 | 191 | 13.2 | 11.5 | 15.0 | 1446 | 214 | 14.8 | 13.0 | 16.7 |
| | Grade 3 | 1449 | 11 | 0.8 | 0.4 | 1.4 | 1446 | 3 | 0.2 | 0.0 | 0.6 |
| | Related | 1449 | 32 | 2.2 | 1.5 | 3.1 | 1446 | 36 | 2.5 | 1.7 | 3.4 |
| | Grade 3 Related | 1449 | 2 | 0.1 | 0.0 | 0.5 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| Diarrhoea | All | 1449 | 57 | 3.9 | 3.0 | 5.1 | 1446 | 45 | 3.1 | 2.3 | 4.1 |
| | Grade 3 | 1449 | 25 | 1.7 | 1.1 | 2.5 | 1446 | 18 | 1.2 | 0.7 | 2.0 |
| | Related | 1449 | 22 | 1.5 | 1.0 | 2.3 | 1446 | 15 | 1.0 | 0.6 | 1.7 |
| | Grade 3 Related | 1449 | 10 | 0.7 | 0.3 | 1.3 | 1446 | 8 | 0.6 | 0.2 | 1.1 |
| Irritability/Fussiness | All | 1449 | 187 | 12.9 | 11.2 | 14.7 | 1446 | 207 | 14.3 | 12.5 | 16.2 |
| | Grade 3 | 1449 | 19 | 1.3 | 0.8 | 2.0 | 1446 | 17 | 1.2 | 0.7 | 1.9 |
| | Related | 1449 | 72 | 5.0 | 3.9 | 6.2 | 1446 | 61 | 4.2 | 3.2 | 5.4 |
| | Grade 3 Related | 1449 | 9 | 0.6 | 0.3 | 1.2 | 1446 | 8 | 0.6 | 0.2 | 1.1 |
| Loss of appetite | All | 1449 | 118 | 8.1 | 6.8 | 9.7 | 1446 | 117 | 8.1 | 6.7 | 9.6 |
| | Grade 3 | 1449 | 1 | 0.1 | 0.0 | 0.4 | 1446 | 4 | 0.3 | 0.1 | 0.7 |
| | Related | 1449 | 39 | 2.7 | 1.9 | 3.7 | 1446 | 34 | 2.4 | 1.6 | 3.3 |
| | Grade 3 Related | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 3 | 0.2 | 0.0 | 0.6 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1449 | 144 | 9.9 | 8.4 | 11.6 | 1446 | 139 | 9.6 | 8.1 | 11.2 |
| | Grade 3 | 1449 | 1 | 0.1 | 0.0 | 0.4 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1449 | 39 | 2.7 | 1.9 | 3.7 | 1446 | 39 | 2.7 | 1.9 | 3.7 |
| | Grade 3 Related | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1449 | 46 | 3.2 | 2.3 | 4.2 | 1446 | 42 | 2.9 | 2.1 | 3.9 |
| | Grade 3 | 1449 | 1 | 0.1 | 0.0 | 0.4 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1449 | 7 | 0.5 | 0.2 | 1.0 | 1446 | 11 | 0.8 | 0.4 | 1.4 |
| | Grade 3 Related | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| Vomiting | All | 1449 | 91 | 6.3 | 5.1 | 7.7 | 1446 | 100 | 6.9 | 5.7 | 8.3 |
| | Grade 3 | 1449 | 30 | 2.1 | 1.4 | 2.9 | 1446 | 29 | 2.0 | 1.3 | 2.9 |
| | Related | 1449 | 26 | 1.8 | 1.2 | 2.6 | 1446 | 12 | 0.8 | 0.4 | 1.4 |
| | Grade 3 Related | 1449 | 10 | 0.7 | 0.3 | 1.3 | 1446 | 4 | 0.3 | 0.1 | 0.7 |

N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once

**Table 218 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Overall/dose** | | | | | | | | | | | |
| Cough/runny nose | All | 2962 | 382 | 12.9 | 11.7 | 14.2 | 2960 | 435 | 14.7 | 13.4 | 16.0 |
| | Grade 3 | 2962 | 20 | 0.7 | 0.4 | 1.0 | 2960 | 7 | 0.2 | 0.1 | 0.5 |
| | Related | 2962 | 70 | 2.4 | 1.8 | 3.0 | 2960 | 66 | 2.2 | 1.7 | 2.8 |
| | Grade 3 Related | 2962 | 7 | 0.2 | 0.1 | 0.5 | 2960 | 1 | 0.0 | 0.0 | 0.2 |
| Diarrhoea | All | 2962 | 137 | 4.6 | 3.9 | 5.4 | 2960 | 132 | 4.5 | 3.7 | 5.3 |
| | Grade 3 | 2962 | 56 | 1.9 | 1.4 | 2.4 | 2960 | 63 | 2.1 | 1.6 | 2.7 |
| | Related | 2962 | 60 | 2.0 | 1.5 | 2.6 | 2960 | 51 | 1.7 | 1.3 | 2.3 |
| | Grade 3 Related | 2962 | 27 | 0.9 | 0.6 | 1.3 | 2960 | 30 | 1.0 | 0.7 | 1.4 |
| Irritability/Fussiness | All | 2962 | 512 | 17.3 | 15.9 | 18.7 | 2960 | 564 | 19.1 | 17.7 | 20.5 |
| | Grade 3 | 2962 | 45 | 1.5 | 1.1 | 2.0 | 2960 | 43 | 1.5 | 1.1 | 2.0 |
| | Related | 2962 | 185 | 6.2 | 5.4 | 7.2 | 2960 | 163 | 5.5 | 4.7 | 6.4 |
| | Grade 3 Related | 2962 | 20 | 0.7 | 0.4 | 1.0 | 2960 | 19 | 0.6 | 0.4 | 1.0 |
| Loss of appetite | All | 2962 | 296 | 10.0 | 8.9 | 11.1 | 2960 | 303 | 10.2 | 9.2 | 11.4 |
| | Grade 3 | 2962 | 4 | 0.1 | 0.0 | 0.3 | 2960 | 7 | 0.2 | 0.1 | 0.5 |
| | Related | 2962 | 102 | 3.4 | 2.8 | 4.2 | 2960 | 92 | 3.1 | 2.5 | 3.8 |
| | Grade 3 Related | 2962 | 3 | 0.1 | 0.0 | 0.3 | 2960 | 5 | 0.2 | 0.1 | 0.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 2962 | 343 | 11.5 | 10.4 | 12.8 | 2960 | 352 | 11.9 | 10.7 | 13.1 |
| | Grade 3 | 2962 | 1 | 0.0 | 0.0 | 0.2 | 2960 | 2 | 0.1 | 0.0 | 0.2 |
| | Related | 2962 | 105 | 3.5 | 2.9 | 4.3 | 2960 | 94 | 3.2 | 2.6 | 3.9 |
| | Grade 3 Related | 2962 | 0 | 0.0 | 0.0 | 0.1 | 2960 | 1 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 2962 | 87 | 2.9 | 2.4 | 3.6 | 2960 | 108 | 3.6 | 3.0 | 4.4 |
| | Grade 3 | 2962 | 1 | 0.0 | 0.0 | 0.2 | 2960 | 2 | 0.1 | 0.0 | 0.2 |
| | Related | 2962 | 24 | 0.8 | 0.5 | 1.2 | 2960 | 26 | 0.9 | 0.6 | 1.3 |
| | Grade 3 Related | 2962 | 0 | 0.0 | 0.0 | 0.1 | 2960 | 1 | 0.0 | 0.0 | 0.2 |
| Vomiting | All | 2962 | 256 | 8.6 | 7.7 | 9.7 | 2960 | 276 | 9.3 | 8.3 | 10.4 |
| | Grade 3 | 2962 | 89 | 3.0 | 2.4 | 3.7 | 2960 | 85 | 2.9 | 2.3 | 3.5 |
| | Related | 2962 | 64 | 2.2 | 1.7 | 2.8 | 2960 | 38 | 1.3 | 0.9 | 1.8 |
| | Grade 3 Related | 2962 | 26 | 0.9 | 0.6 | 1.3 | 2960 | 17 | 0.6 | 0.3 | 0.9 |
| **Overall/subject** | | | | | | | | | | | |
| Cough/runny nose | All | 1513 | 313 | 20.7 | 18.7 | 22.8 | 1514 | 366 | 24.2 | 22.0 | 26.4 |
| | Grade 3 | 1513 | 19 | 1.3 | 0.8 | 2.0 | 1514 | 7 | 0.5 | 0.2 | 1.0 |
| | Related | 1513 | 64 | 4.2 | 3.3 | 5.4 | 1514 | 58 | 3.8 | 2.9 | 4.9 |
| | Grade 3 Related | 1513 | 7 | 0.5 | 0.2 | 1.0 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| Diarrhoea | All | 1513 | 127 | 8.4 | 7.0 | 9.9 | 1514 | 123 | 8.1 | 6.8 | 9.6 |
| | Grade 3 | 1513 | 55 | 3.6 | 2.8 | 4.7 | 1514 | 60 | 4.0 | 3.0 | 5.1 |
| | Related | 1513 | 58 | 3.8 | 2.9 | 4.9 | 1514 | 49 | 3.2 | 2.4 | 4.3 |
| | Grade 3 Related | 1513 | 26 | 1.7 | 1.1 | 2.5 | 1514 | 29 | 1.9 | 1.3 | 2.7 |
| Irritability/Fussiness | All | 1513 | 415 | 27.4 | 25.2 | 29.8 | 1514 | 448 | 29.6 | 27.3 | 32.0 |
| | Grade 3 | 1513 | 43 | 2.8 | 2.1 | 3.8 | 1514 | 39 | 2.6 | 1.8 | 3.5 |
| | Related | 1513 | 158 | 10.4 | 8.9 | 12.1 | 1514 | 144 | 9.5 | 8.1 | 11.1 |
| | Grade 3 Related | 1513 | 18 | 1.2 | 0.7 | 1.9 | 1514 | 18 | 1.2 | 0.7 | 1.9 |
| Loss of appetite | All | 1513 | 253 | 16.7 | 14.9 | 18.7 | 1514 | 250 | 16.5 | 14.7 | 18.5 |
| | Grade 3 | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 7 | 0.5 | 0.2 | 1.0 |
| | Related | 1513 | 90 | 5.9 | 4.8 | 7.3 | 1514 | 83 | 5.5 | 4.4 | 6.8 |
| | Grade 3 Related | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 5 | 0.3 | 0.1 | 0.8 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1513 | 302 | 20.0 | 18.0 | 22.1 | 1514 | 313 | 20.7 | 18.7 | 22.8 |
| | Grade 3 | 1513 | 1 | 0.1 | 0.0 | 0.4 | 1514 | 2 | 0.1 | 0.0 | 0.5 |
| | Related | 1513 | 101 | 6.7 | 5.5 | 8.1 | 1514 | 91 | 6.0 | 4.9 | 7.3 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1513 | 83 | 5.5 | 4.4 | 6.8 | 1514 | 104 | 6.9 | 5.6 | 8.3 |
| | Grade 3 | 1513 | 1 | 0.1 | 0.0 | 0.4 | 1514 | 2 | 0.1 | 0.0 | 0.5 |
| | Related | 1513 | 24 | 1.6 | 1.0 | 2.4 | 1514 | 26 | 1.7 | 1.1 | 2.5 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| Vomiting | All | 1513 | 213 | 14.1 | 12.4 | 15.9 | 1514 | 232 | 15.3 | 13.5 | 17.2 |
| | Grade 3 | 1513 | 80 | 5.3 | 4.2 | 6.5 | 1514 | 75 | 5.0 | 3.9 | 6.2 |
| | Related | 1513 | 57 | 3.8 | 2.9 | 4.9 | 1514 | 33 | 2.2 | 1.5 | 3.0 |
| | Grade 3 Related | 1513 | 23 | 1.5 | 1.0 | 2.3 | 1514 | 16 | 1.1 | 0.6 | 1.7 |

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

**Table 219 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Drowsiness | All | 153 | 37 | 24.2 | 17.6 | 31.8 | 153 | 26 | 17.0 | 11.4 | 23.9 |
| | Grade 3 | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 9 | 5.9 | 2.7 | 10.9 | 153 | 6 | 3.9 | 1.5 | 8.3 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Gastrointestinal | All | 153 | 36 | 23.5 | 17.1 | 31.1 | 153 | 31 | 20.3 | 14.2 | 27.5 |
| | Grade 3 | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 14 | 9.2 | 5.1 | 14.9 | 153 | 9 | 5.9 | 2.7 | 10.9 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 5 | 3.3 | 1.1 | 7.5 |
| Irritability/Fussiness | All | 153 | 44 | 28.8 | 21.7 | 36.6 | 153 | 40 | 26.1 | 19.4 | 33.9 |
| | Grade 3 | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 4 | 2.6 | 0.7 | 6.6 |
| | Related | 153 | 15 | 9.8 | 5.6 | 15.7 | 153 | 5 | 3.3 | 1.1 | 7.5 |
| | Grade 3 Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 3 | 2.0 | 0.4 | 5.6 |
| Loss of appetite | All | 153 | 31 | 20.3 | 14.2 | 27.5 | 153 | 23 | 15.0 | 9.8 | 21.7 |
| | Grade 3 | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 13 | 8.5 | 4.6 | 14.1 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 10 | 6.5 | 3.2 | 11.7 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 8 | 5.2 | 2.3 | 10.0 | 153 | 4 | 2.6 | 0.7 | 6.6 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| Temperature/(Axillary) (°C) according GSK scale | All | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| **Dose 2** | | | | | | | | | | | |
| Drowsiness | All | 150 | 21 | 14.0 | 8.9 | 20.6 | 151 | 23 | 15.2 | 9.9 | 22.0 |
| | Grade 3 | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 6 | 4.0 | 1.5 | 8.5 | 151 | 7 | 4.6 | 1.9 | 9.3 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Gastrointestinal | All | 150 | 20 | 13.3 | 8.3 | 19.8 | 151 | 18 | 11.9 | 7.2 | 18.2 |
| | Grade 3 | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 6 | 4.0 | 1.5 | 8.5 | 151 | 7 | 4.6 | 1.9 | 9.3 |
| | Grade 3 Related | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Irritability/Fussiness | All | 150 | 28 | 18.7 | 12.8 | 25.8 | 151 | 26 | 17.2 | 11.6 | 24.2 |
| | Grade 3 | 150 | 4 | 2.7 | 0.7 | 6.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 150 | 9 | 6.0 | 2.8 | 11.1 | 151 | 5 | 3.3 | 1.1 | 7.6 |
| | Grade 3 Related | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Loss of appetite | All | 150 | 21 | 14.0 | 8.9 | 20.6 | 151 | 16 | 10.6 | 6.2 | 16.6 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 9 | 6.0 | 2.8 | 11.1 | 151 | 5 | 3.3 | 1.1 | 7.6 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 150 | 8 | 5.3 | 2.3 | 10.2 | 151 | 12 | 7.9 | 4.2 | 13.5 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 3 | 2.0 | 0.4 | 5.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| Temperature/(Axillary) (°C) accordingGSK scale | All | 150 | 3 | 2.0 | 0.4 | 5.7 | 151 | 5 | 3.3 | 1.1 | 7.6 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |

N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once

**Table 220 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort-Immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Overall/dose | | | | | | | | | | | |
| Drowsiness | All | 303 | 58 | 19.1 | 14.9 | 24.0 | 304 | 49 | 16.1 | 12.2 | 20.7 |
| | Grade 3 | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Related | 303 | 15 | 5.0 | 2.8 | 8.0 | 304 | 13 | 4.3 | 2.3 | 7.2 |
| | Grade 3 Related | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Gastrointestinal | All | 303 | 56 | 18.5 | 14.3 | 23.3 | 304 | 49 | 16.1 | 12.2 | 20.7 |
| | Grade 3 | 303 | 2 | 0.7 | 0.1 | 2.4 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| | Related | 303 | 20 | 6.6 | 4.1 | 10.0 | 304 | 16 | 5.3 | 3.0 | 8.4 |
| | Grade 3 Related | 303 | 2 | 0.7 | 0.1 | 2.4 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Medical attention | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 5 | 1.6 | 0.5 | 3.8 |
| Irritability/ Fussiness | All | 303 | 72 | 23.8 | 19.1 | 29.0 | 304 | 66 | 21.7 | 17.2 | 26.8 |
| | Grade 3 | 303 | 6 | 2.0 | 0.7 | 4.3 | 304 | 5 | 1.6 | 0.5 | 3.8 |
| | Related | 303 | 24 | 7.9 | 5.1 | 11.6 | 304 | 10 | 3.3 | 1.6 | 6.0 |
| | Grade 3 Related | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| | Medical attention | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 3 | 1.0 | 0.2 | 2.9 |
| Loss of appetite | All | 303 | 52 | 17.2 | 13.1 | 21.9 | 304 | 39 | 12.8 | 9.3 | 17.1 |
| | Grade 3 | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| | Related | 303 | 22 | 7.3 | 4.6 | 10.8 | 304 | 7 | 2.3 | 0.9 | 4.7 |
| | Grade 3 Related | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 2 | 0.7 | 0.1 | 2.4 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Temperature/ (Axillary) (°C) according Chinese scale | All | 303 | 20 | 6.6 | 4.1 | 10.0 | 304 | 22 | 7.2 | 4.6 | 10.8 |
| | Grade 3 | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Related | 303 | 11 | 3.6 | 1.8 | 6.4 | 304 | 5 | 1.6 | 0.5 | 3.8 |
| | Grade 3 Related | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Temperature/ (Axillary) (°C) according GSK scale | All | 303 | 6 | 2.0 | 0.7 | 4.3 | 304 | 7 | 2.3 | 0.9 | 4.7 |
| | Grade 3 | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Related | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Grade 3 Related | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | | | | | | | | | | | |
| Overall/subject | | | | | | | | | | | |
| Drowsiness | All | 153 | 44 | 28.8 | 21.7 | 36.6 | 153 | 38 | 24.8 | 18.2 | 32.5 |
| | Grade 3 | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 11 | 7.2 | 3.6 | 12.5 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Gastrointestinal | All | 153 | 43 | 28.1 | 21.1 | 35.9 | 153 | 38 | 24.8 | 18.2 | 32.5 |
| | Grade 3 | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 17 | 11.1 | 6.6 | 17.2 | 153 | 15 | 9.8 | 5.6 | 15.7 |
| | Grade 3 Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 5 | 3.3 | 1.1 | 7.5 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Irritability/ Fussiness | All | 153 | 56 | 36.6 | 29.0 | 44.8 | 153 | 52 | 34.0 | 26.5 | 42.1 |
| | Grade 3 | 153 | 5 | 3.3 | 1.1 | 7.5 | 153 | 4 | 2.6 | 0.7 | 6.6 |
| | Related | 153 | 18 | 11.8 | 7.1 | 18.0 | 153 | 10 | 6.5 | 3.2 | 11.7 |
| | Grade 3 Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 3 | 2.0 | 0.4 | 5.6 |
| Loss of appetite | All | 153 | 43 | 28.1 | 21.1 | 35.9 | 153 | 32 | 20.9 | 14.8 | 28.2 |
| | Grade 3 | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 17 | 11.1 | 6.6 | 17.2 | 153 | 7 | 4.6 | 1.9 | 9.2 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Temperature/ (Axillary) (°C) according Chinese scale | All | 153 | 18 | 11.8 | 7.1 | 18.0 | 153 | 20 | 13.1 | 8.2 | 19.5 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 11 | 7.2 | 3.6 | 12.5 | 153 | 5 | 3.3 | 1.1 | 7.5 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Temperature/ (Axillary) (°C) according GSK scale | All | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 7 | 4.6 | 1.9 | 9.2 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |

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

### 11.6.1.4. Unsolicited adverse events

**Table 221 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)**

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 310 | 18.6 | 16.8 | 20.6 | 368 | 22.1 | 20.1 | 24.1 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Heart disease congenital (10019273) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Hydrocele (10020488) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Thalassaemia (10043388) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Abdominal pain (10000081) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Constipation (10010774) | 15 | 0.9 | 0.5 | 1.5 | 9 | 0.5 | 0.2 | 1.0 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.4 | 6 | 0.4 | 0.1 | 0.8 |
| | Dyspepsia (10013946) | 8 | 0.5 | 0.2 | 0.9 | 7 | 0.4 | 0.2 | 0.9 |
| | Enteritis (10014866) | 6 | 0.4 | 0.1 | 0.8 | 14 | 0.8 | 0.5 | 1.4 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Mouth ulceration (10028034) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Vomiting (10047700) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Pyrexia (10037660) | 13 | 0.8 | 0.4 | 1.3 | 27 | 1.6 | 1.1 | 2.3 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hypersensitivity (10020751) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchitis (10006451) | 18 | 1.1 | 0.6 | 1.7 | 27 | 1.6 | 1.1 | 2.3 |
| | Bronchopneumonia (10006469) | 9 | 0.5 | 0.2 | 1.0 | 11 | 0.7 | 0.3 | 1.2 |
| | Candidiasis (10007152) | 7 | 0.4 | 0.2 | 0.9 | 6 | 0.4 | 0.1 | 0.8 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Cytomegalovirus infection (10011831) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Exanthema subitum (10015586) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis (10017888) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Nasopharyngitis (10028810) | 103 | 6.2 | 5.1 | 7.4 | 123 | 7.4 | 6.2 | 8.7 |
| | Otitis media (10033078) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Pharyngitis (10034835) | 6 | 0.4 | 0.1 | 0.8 | 8 | 0.5 | 0.2 | 0.9 |
| | Pneumonia (10035664) | 3 | 0.2 | 0.0 | 0.5 | 4 | 0.2 | 0.1 | 0.6 |
| | Pneumonia klebsiella (10035717) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tonsillitis (10044008) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.4 | 5 | 0.3 | 0.1 | 0.7 |
| | Tracheobronchitis (10044314) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 119 | 7.1 | 6.0 | 8.5 | 124 | 7.4 | 6.2 | 8.8 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Varicella (10046980) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.5 | 0.2 | 1.0 | 7 | 0.4 | 0.2 | 0.9 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 7 | 0.4 | 0.2 | 0.9 | 16 | 1.0 | 0.5 | 1.6 |
| | Nasal congestion (10028735) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |
| | Dermatitis allergic (10012434) | 6 | 0.4 | 0.1 | 0.8 | 3 | 0.2 | 0.0 | 0.5 |
| | Dermatitis diaper (10012444) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Eczema (10014184) | 1 | 0.1 | 0.0 | 0.3 | 4 | 0.2 | 0.1 | 0.6 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rash (10037844) | 3 | 0.2 | 0.0 | 0.5 | 5 | 0.3 | 0.1 | 0.7 |

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

**Table 222 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)**

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 356 | 10.9 | 9.9 | 12.0 | 420 | 12.9 | 11.7 | 14.1 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Heart disease congenital (10019273) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Hydrocele (10020488) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Thalassaemia (10043388) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Abdominal pain (10000081) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Constipation (10010774) | 16 | 0.5 | 0.3 | 0.8 | 10 | 0.3 | 0.1 | 0.6 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.2 | 6 | 0.2 | 0.1 | 0.4 |
| | Dyspepsia (10013946) | 8 | 0.2 | 0.1 | 0.5 | 7 | 0.2 | 0.1 | 0.4 |
| | Enteritis (10014866) | 6 | 0.2 | 0.1 | 0.4 | 14 | 0.4 | 0.2 | 0.7 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Mouth ulceration (10028034) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Vomiting (10047700) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Pyrexia (10037660) | 13 | 0.4 | 0.2 | 0.7 | 27 | 0.8 | 0.5 | 1.2 |

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hypersensitivity (10020751) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Bronchitis (10006451) | 18 | 0.6 | 0.3 | 0.9 | 27 | 0.8 | 0.5 | 1.2 |
| | Bronchopneumonia (10006469) | 9 | 0.3 | 0.1 | 0.5 | 11 | 0.3 | 0.2 | 0.6 |
| | Candidiasis (10007152) | 7 | 0.2 | 0.1 | 0.4 | 7 | 0.2 | 0.1 | 0.4 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Cytomegalovirus infection (10011831) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Exanthema subitum (10015586) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Gastroenteritis (10017888) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 110 | 3.4 | 2.8 | 4.0 | 131 | 4.0 | 3.4 | 4.7 |
| | Otitis media (10033078) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Pharyngitis (10034835) | 6 | 0.2 | 0.1 | 0.4 | 8 | 0.2 | 0.1 | 0.5 |
| | Pneumonia (10035664) | 3 | 0.1 | 0.0 | 0.3 | 4 | 0.1 | 0.0 | 0.3 |
| | Pneumonia klebsiella (10035717) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Tonsillitis (10044008) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.2 | 5 | 0.2 | 0.0 | 0.4 |
| | Tracheobronchitis (10044314) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Upper respiratory tract infection (10046306) | 126 | 3.9 | 3.2 | 4.6 | 134 | 4.1 | 3.5 | 4.8 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Varicella (10046980) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.3 | 0.1 | 0.5 | 8 | 0.2 | 0.1 | 0.5 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 8 | 0.2 | 0.1 | 0.5 | 16 | 0.5 | 0.3 | 0.8 |
| | Nasal congestion (10028735) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |
| | Dermatitis allergic (10012434) | 6 | 0.2 | 0.1 | 0.4 | 3 | 0.1 | 0.0 | 0.3 |
| | Dermatitis diaper (10012444) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Eczema (10014184) | 1 | 0.0 | 0.0 | 0.2 | 4 | 0.1 | 0.0 | 0.3 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rash (10037844) | 3 | 0.1 | 0.0 | 0.3 | 5 | 0.2 | 0.0 | 0.4 |

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

## Table 223 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |

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

## Table 224 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |

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

## Table 225 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 8 | 0.5 | 0.2 | 0.9 | 7 | 0.4 | 0.2 | 0.9 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.3 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Dyspepsia (10013946) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.1 | 0.0 | 0.3 | 4 | 0.2 | 0.1 | 0.6 |
| | Upper respiratory tract infection (10046306) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |

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

## Table 226 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 8 | 0.2 | 0.1 | 0.5 | 7 | 0.2 | 0.1 | 0.4 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Dyspepsia (10013946) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.0 | 0.0 | 0.2 | 4 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |

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

**Table 227 Percentage of subjects with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with reported during the entire study period (Total vaccinated cohort)**

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 445 | 26.7 | 24.6 | 28.9 | 525 | 31.5 | 29.3 | 33.8 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Lymphadenitis (10025188) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Cardiac disorders (10007541) | Myocarditis (10028606) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Cortical dysplasia (10070666) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 3 | 0.2 | 0.0 | 0.5 | 1 | 0.1 | 0.0 | 0.3 |
| | Heart disease congenital (10019273) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Hydrocele (10020488) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Patent ductus arteriosus (10034130) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Thalassaemia (10043388) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Thalassaemia beta (10043391) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Ventricular septal defect (10047298) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Abdominal pain (10000081) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Constipation (10010774) | 15 | 0.9 | 0.5 | 1.5 | 9 | 0.5 | 0.2 | 1.0 |
| | Diarrhoea (10012735) | 4 | 0.2 | 0.1 | 0.6 | 11 | 0.7 | 0.3 | 1.2 |
| | Dyspepsia (10013946) | 8 | 0.5 | 0.2 | 0.9 | 8 | 0.5 | 0.2 | 0.9 |
| | Enteritis (10014866) | 44 | 2.6 | 1.9 | 3.5 | 73 | 4.4 | 3.4 | 5.5 |
| | Food poisoning (10016952) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Gastrointestinal disorder (10017944) | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Inguinal hernia (10022016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Inguinal hernia, obstructive (10022021) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Intestinal obstruction (10022687) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Intussusception (10022863) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Mouth ulceration (10028034) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Vomiting (10047700) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| General disorders and administration site conditions (10018065) | Death (10011906) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Drowning (10013647) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Multi-organ failure (10028154) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Pyrexia (10037660) | 15 | 0.9 | 0.5 | 1.5 | 27 | 1.6 | 1.1 | 2.3 |
| Hepatobiliary disorders (10019805) | Hepatic function abnormal (10019670) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hypersensitivity (10020751) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 5 | 0.3 | 0.1 | 0.7 | 2 | 0.1 | 0.0 | 0.4 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchiolitis (10006448) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchitis (10006451) | 81 | 4.9 | 3.9 | 6.0 | 104 | 6.2 | 5.1 | 7.5 |
| | Bronchopneumonia (10006469) | 58 | 3.5 | 2.7 | 4.5 | 62 | 3.7 | 2.9 | 4.7 |
| | Candidiasis (10007152) | 8 | 0.5 | 0.2 | 0.9 | 7 | 0.4 | 0.2 | 0.9 |
| | Central nervous system infection (10061036) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Cytomegalovirus infection (10011831) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Diarrhoea infectious (10012742) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Exanthema subitum (10015586) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis (10017888) | 2 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.4 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Hand-foot-and-mouth disease (10019113) | 5 | 0.3 | 0.1 | 0.7 | 4 | 0.2 | 0.1 | 0.6 |
| | Herpangina (10019936) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Infectious mononucleosis (10021914) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Laryngitis (10023874) | 2 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.4 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Meningitis (10027199) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 111 | 6.7 | 5.5 | 8.0 | 127 | 7.6 | 6.4 | 9.0 |
| | Otitis media (10033078) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Pharyngitis (10034835) | 9 | 0.5 | 0.2 | 1.0 | 16 | 1.0 | 0.5 | 1.6 |
| | Pneumonia (10035664) | 15 | 0.9 | 0.5 | 1.5 | 14 | 0.8 | 0.5 | 1.4 |
| | Pneumonia klebsiella (10035717) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Shigella infection (10054178) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tonsillitis (10044008) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Tracheitis (10044302) | 7 | 0.4 | 0.2 | 0.9 | 9 | 0.5 | 0.2 | 1.0 |
| | Tracheobronchitis (10044314) | 5 | 0.3 | 0.1 | 0.7 | 1 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 136 | 8.2 | 6.9 | 9.6 | 151 | 9.1 | 7.7 | 10.5 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Varicella (10046980) | 2 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.3 |
| Injury, poisoning and procedural complications (10022117) | Brain contusion (10052346) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Brain herniation (10006126) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Skull fracture (10061365) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.5 | 0.2 | 1.0 | 8 | 0.5 | 0.2 | 0.9 |
| | Liver function test abnormal (10024690) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Dehydration (10012174) | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| | Hypokalaemia (10021015) | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| | Hyponatraemia (10021036) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104) | Acute lymphocytic leukaemia (10000846) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Histiocytosis haematophagic (10048595) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Cerebral haematoma (10053942) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Convulsion (10010904) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Epilepsy (10015037) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Febrile convulsion (10016284) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Subarachnoid haemorrhage (10042316) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Renal and urinary disorders (10038359) | Hydronephrosis (10020524) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Ureteric stenosis (10046411) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Asphyxia (10003497) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Asthma (10003553) | 3 | 0.2 | 0.0 | 0.5 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Cough (10011224) | 7 | 0.4 | 0.2 | 0.9 | 18 | 1.1 | 0.6 | 1.7 |
| | Nasal congestion (10028735) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Respiratory failure (10038695) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rhinorrhoea (10039101) | 3 | 0.2 | 0.0 | 0.5 | 4 | 0.2 | 0.1 | 0.6 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |
| | Dermatitis allergic (10012434) | 8 | 0.5 | 0.2 | 0.9 | 3 | 0.2 | 0.0 | 0.5 |
| | Dermatitis diaper (10012444) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Eczema (10014184) | 1 | 0.1 | 0.0 | 0.3 | 4 | 0.2 | 0.1 | 0.6 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rash (10037844) | 3 | 0.2 | 0.0 | 0.5 | 5 | 0.3 | 0.1 | 0.7 |
| | Urticaria (10046735) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |

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

**Table 228 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| **At least one symptom** | | 258 | 17.1 | 15.2 | 19.0 | 312 | 20.6 | 18.6 | 22.7 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.5 |
| | Heart disease congenital (10019273) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.5 | 3 | 0.2 | 0.0 | 0.6 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.5 | 0 | 0.0 | 0.0 | 0.2 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Abdominal pain (10000081) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Constipation (10010774) | 15 | 1.0 | 0.6 | 1.6 | 9 | 0.6 | 0.3 | 1.1 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.5 | 6 | 0.4 | 0.1 | 0.9 |
| | Dyspepsia (10013946) | 7 | 0.5 | 0.2 | 1.0 | 6 | 0.4 | 0.1 | 0.9 |
| | Enteritis (10014866) | 5 | 0.3 | 0.1 | 0.8 | 11 | 0.7 | 0.4 | 1.3 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.5 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Mouth ulceration (10028034) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Vomiting (10047700) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Pyrexia (10037660) | 10 | 0.7 | 0.3 | 1.2 | 24 | 1.6 | 1.0 | 2.3 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Hypersensitivity (10020751) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.5 | 0 | 0.0 | 0.0 | 0.2 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Bronchitis (10006451) | 16 | 1.1 | 0.6 | 1.7 | 22 | 1.5 | 0.9 | 2.2 |
| | Bronchopneumonia (10006469) | 7 | 0.5 | 0.2 | 1.0 | 9 | 0.6 | 0.3 | 1.1 |
| | Candidiasis (10007152) | 6 | 0.4 | 0.1 | 0.9 | 6 | 0.4 | 0.1 | 0.9 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Cytomegalovirus infection (10011831) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Exanthema subitum (10015586) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis (10017888) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Nasopharyngitis (10028810) | 83 | 5.5 | 4.4 | 6.8 | 108 | 7.1 | 5.9 | 8.5 |
| | Pharyngitis (10034835) | 5 | 0.3 | 0.1 | 0.8 | 8 | 0.5 | 0.2 | 1.0 |
| | Pneumonia (10035664) | 1 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.5 |
| | Pneumonia klebsiella (10035717) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Tonsillitis (10044008) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.5 | 3 | 0.2 | 0.0 | 0.6 |
| | Tracheobronchitis (10044314) | 4 | 0.3 | 0.1 | 0.7 | 1 | 0.1 | 0.0 | 0.4 |
| | Upper respiratory tract infection (10046306) | 89 | 5.9 | 4.8 | 7.2 | 98 | 6.5 | 5.3 | 7.8 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.5 | 0 | 0.0 | 0.0 | 0.2 |
| | Varicella (10046980) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.6 | 0.3 | 1.1 | 7 | 0.5 | 0.2 | 1.0 |
| Metabolism and nutrition disorders (10027433) | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.5 |

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 6 | 0.4 | 0.1 | 0.9 | 13 | 0.9 | 0.5 | 1.5 |
| | Nasal congestion (10028735) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.5 | 3 | 0.2 | 0.0 | 0.6 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 3 | 0.2 | 0.0 | 0.6 | 1 | 0.1 | 0.0 | 0.4 |
| | Dermatitis allergic (10012434) | 6 | 0.4 | 0.1 | 0.9 | 3 | 0.2 | 0.0 | 0.6 |
| | Eczema (10014184) | 1 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.6 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Rash (10037844) | 3 | 0.2 | 0.0 | 0.6 | 5 | 0.3 | 0.1 | 0.8 |

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

**Table 229 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort-except immunogenicity sub-cohort 2)**

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 292 | 9.9 | 8.8 | 11.0 | 354 | 12.0 | 10.8 | 13.2 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Heart disease congenital (10019273) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Abdominal pain (10000081) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Constipation (10010774) | 16 | 0.5 | 0.3 | 0.9 | 10 | 0.3 | 0.2 | 0.6 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.2 | 6 | 0.2 | 0.1 | 0.4 |
| | Dyspepsia (10013946) | 7 | 0.2 | 0.1 | 0.5 | 6 | 0.2 | 0.1 | 0.4 |
| | Enteritis (10014866) | 5 | 0.2 | 0.1 | 0.4 | 11 | 0.4 | 0.2 | 0.7 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Mouth ulceration (10028034) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Vomiting (10047700) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Pyrexia (10037660) | 10 | 0.3 | 0.2 | 0.6 | 24 | 0.8 | 0.5 | 1.2 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hypersensitivity (10020751) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Bronchitis (10006451) | 16 | 0.5 | 0.3 | 0.9 | 22 | 0.7 | 0.5 | 1.1 |

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Bronchopneumonia (10006469) | 7 | 0.2 | 0.1 | 0.5 | 9 | 0.3 | 0.1 | 0.6 |
| | Candidiasis (10007152) | 6 | 0.2 | 0.1 | 0.4 | 7 | 0.2 | 0.1 | 0.5 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Cytomegalovirus infection (10011831) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Exanthema subitum (10015586) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Gastroenteritis (10017888) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 89 | 3.0 | 2.4 | 3.7 | 115 | 3.9 | 3.2 | 4.6 |
| | Pharyngitis (10034835) | 5 | 0.2 | 0.1 | 0.4 | 8 | 0.3 | 0.1 | 0.5 |
| | Pneumonia (10035664) | 1 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.2 |
| | Pneumonia klebsiella (10035717) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Tonsillitis (10044008) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Tracheobronchitis (10044314) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |
| | Upper respiratory tract infection (10046306) | 94 | 3.2 | 2.6 | 3.9 | 106 | 3.6 | 2.9 | 4.3 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Varicella (10046980) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.3 | 0.1 | 0.6 | 8 | 0.3 | 0.1 | 0.5 |
| Metabolism and nutrition disorders (10027433) | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 7 | 0.2 | 0.1 | 0.5 | 13 | 0.4 | 0.2 | 0.7 |
| | Nasal congestion (10028735) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 3 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |
| | Dermatitis allergic (10012434) | 6 | 0.2 | 0.1 | 0.4 | 3 | 0.1 | 0.0 | 0.3 |
| | Eczema (10014184) | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rash (10037844) | 3 | 0.1 | 0.0 | 0.3 | 5 | 0.2 | 0.1 | 0.4 |

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

**Table 230 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 1 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.5 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |

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

**Table 231 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 1 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.2 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |

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

## Table 232 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 5 | 0.3 | 0.1 | 0.8 | 6 | 0.4 | 0.1 | 0.9 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.5 | 1 | 0.1 | 0.0 | 0.4 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Dyspepsia (10013946) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.6 |
| | Upper respiratory tract infection (10046306) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |

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

## Table 233 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 5 | 0.2 | 0.1 | 0.4 | 6 | 0.2 | 0.1 | 0.4 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Dyspepsia (10013946) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |

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

**Table 234 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV N = 153 | | | | Placebo N = 153 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 52 | 34.0 | 26.5 | 42.1 | 56 | 36.6 | 29.0 | 44.8 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.7 | 0.0 | 3.6 | 1 | 0.7 | 0.0 | 3.6 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| Congenital, familial and genetic disorders (10010331) | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 1.3 | 0.2 | 4.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Hydrocele (10020488) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Thalassaemia (10043388) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| Gastrointestinal disorders (10017947) | Dyspepsia (10013946) | 1 | 0.7 | 0.0 | 3.6 | 1 | 0.7 | 0.0 | 3.6 |
| | Enteritis (10014866) | 1 | 0.7 | 0.0 | 3.6 | 3 | 2.0 | 0.4 | 5.6 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| General disorders and administration site conditions (10018065) | Pyrexia (10037660) | 3 | 2.0 | 0.4 | 5.6 | 3 | 2.0 | 0.4 | 5.6 |
| Infections and infestations (10021881) | Bronchitis (10006451) | 2 | 1.3 | 0.2 | 4.6 | 5 | 3.3 | 1.1 | 7.5 |
| | Bronchopneumonia (10006469) | 2 | 1.3 | 0.2 | 4.6 | 2 | 1.3 | 0.2 | 4.6 |
| | Candidiasis (10007152) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Nasopharyngitis (10028810) | 20 | 13.1 | 8.2 | 19.5 | 15 | 9.8 | 5.6 | 15.7 |
| | Otitis media (10033078) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Pharyngitis (10034835) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Pneumonia (10035664) | 2 | 1.3 | 0.2 | 4.6 | 2 | 1.3 | 0.2 | 4.6 |
| | Tracheitis (10044302) | 0 | 0.0 | 0.0 | 2.4 | 2 | 1.3 | 0.2 | 4.6 |
| | Upper respiratory tract infection (10046306) | 30 | 19.6 | 13.6 | 26.8 | 26 | 17.0 | 11.4 | 23.9 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 1 | 0.7 | 0.0 | 3.6 | 3 | 2.0 | 0.4 | 5.6 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Dermatitis diaper (10012444) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Eczema (10014184) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |

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

**Table 235 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort-Immunogenicity sub-cohort 2)**

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 64 | 21.1 | 16.7 | 26.2 | 66 | 21.7 | 17.2 | 26.8 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.3 | 0.0 | 1.8 | 1 | 0.3 | 0.0 | 1.8 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| Congenital, familial and genetic disorders (10010331) | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 0.7 | 0.1 | 2.4 | 0 | 0.0 | 0.0 | 1.2 |
| | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Hydrocele (10020488) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Thalassaemia (10043388) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| Gastrointestinal disorders (10017947) | Dyspepsia (10013946) | 1 | 0.3 | 0.0 | 1.8 | 1 | 0.3 | 0.0 | 1.8 |
| | Enteritis (10014866) | 1 | 0.3 | 0.0 | 1.8 | 3 | 1.0 | 0.2 | 2.9 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| General disorders and administration site conditions (10018065) | Pyrexia (10037660) | 3 | 1.0 | 0.2 | 2.9 | 3 | 1.0 | 0.2 | 2.9 |
| Infections and infestations (10021881) | Bronchitis (10006451) | 2 | 0.7 | 0.1 | 2.4 | 5 | 1.6 | 0.5 | 3.8 |
| | Bronchopneumonia (10006469) | 2 | 0.7 | 0.1 | 2.4 | 2 | 0.7 | 0.1 | 2.4 |
| | Candidiasis (10007152) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Nasopharyngitis (10028810) | 21 | 6.9 | 4.3 | 10.4 | 16 | 5.3 | 3.0 | 8.4 |
| | Otitis media (10033078) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Pharyngitis (10034835) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Pneumonia (10035664) | 2 | 0.7 | 0.1 | 2.4 | 2 | 0.7 | 0.1 | 2.4 |
| | Tracheitis (10044302) | 0 | 0.0 | 0.0 | 1.2 | 2 | 0.7 | 0.1 | 2.4 |
| | Upper respiratory tract infection (10046306) | 32 | 10.6 | 7.3 | 14.6 | 28 | 9.2 | 6.2 | 13.0 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 1 | 0.3 | 0.0 | 1.8 | 3 | 1.0 | 0.2 | 2.9 |

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Dermatitis diaper (10012444) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Eczema (10014184) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |

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

## Table 236 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | HRV N = 153 | | | | Placebo N = 153 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |

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

## Table 237 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |

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

**Table 238 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV N = 153 | | | | Placebo N = 153 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 3 | 2.0 | 0.4 | 5.6 | 1 | 0.7 | 0.0 | 3.6 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Upper respiratory tract infection (10046306) | 3 | 2.0 | 0.4 | 5.6 | 0 | 0.0 | 0.0 | 2.4 |

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

**Table 239 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 3 | 1.0 | 0.2 | 2.9 | 1 | 0.3 | 0.0 | 1.8 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Upper respiratory tract infection (10046306) | 3 | 1.0 | 0.2 | 2.9 | 0 | 0.0 | 0.0 | 1.2 |

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

## 11.6.2. Serious adverse events

### 11.6.2.1. Fatal events

**Table 240 Listings of fatalities from dose 1 of HRV or Placebo up to visit 7 (Total vaccinated cohort)**

### 11.6.2.2. Non-fatal events

Refer section 14.1.

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

### Table 241 Percentage of subjects reporting the occurrence of AEs/SAEs leading to drop out from the study classified by MedDRA Primary System Organ Class and Preferred Term during the study period (Total vaccinated cohort)

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 8 | 0.5 | 0.2 | 0.9 | 10 | 0.6 | 0.3 | 1.1 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Cortical dysplasia (10070666) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Gastrointestinal disorders (10017947) | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| General disorders and administration site conditions (10018065) | Drowning (10013647) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Multi-organ failure (10028154) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| Infections and infestations (10021881) | Bronchitis (10006451) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchopneumonia (10006469) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Central nervous system infection (10061036) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Meningitis (10027199) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 2 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.4 |
| Injury, poisoning and procedural complications (10022117) | Brain contusion (10052346) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Brain herniation (10006126) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Skull fracture (10061365) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104) | Acute lymphocytic leukaemia (10000846) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Cerebral haematoma (10053942) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Subarachnoid haemorrhage (10042316) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Asphyxia (10003497) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory failure (10038695) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |

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

## 11.6.4. Concomitant medications /vaccinations

### Table 242 Incidence of concomitant medication within the 8-day (Days 0-7) post vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 1513 | 73 | 4.8 | 3.8 | 6.0 | 1514 | 109 | 7.2 | 5.9 | 8.6 |
| Any antipyretic | 1513 | 9 | 0.6 | 0.3 | 1.1 | 1514 | 20 | 1.3 | 0.8 | 2.0 |
| Prophylactic antipyretic | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1513 | 18 | 1.2 | 0.7 | 1.9 | 1514 | 24 | 1.6 | 1.0 | 2.3 |
| **Dose 2** | | | | | | | | | | |
| Any | 1449 | 84 | 5.8 | 4.7 | 7.1 | 1446 | 80 | 5.5 | 4.4 | 6.8 |
| Any antipyretic | 1449 | 12 | 0.8 | 0.4 | 1.4 | 1446 | 14 | 1.0 | 0.5 | 1.6 |
| Prophylactic antipyretic | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 0 | 0.0 | 0.0 | 0.3 |
| Any antibiotic | 1449 | 23 | 1.6 | 1.0 | 2.4 | 1446 | 33 | 2.3 | 1.6 | 3.2 |
| **Overall/dose** | | | | | | | | | | |
| Any | 2962 | 157 | 5.3 | 4.5 | 6.2 | 2960 | 189 | 6.4 | 5.5 | 7.3 |
| Any antipyretic | 2962 | 21 | 0.7 | 0.4 | 1.1 | 2960 | 34 | 1.1 | 0.8 | 1.6 |
| Prophylactic antipyretic | 2962 | 0 | 0.0 | 0.0 | 0.1 | 2960 | 0 | 0.0 | 0.0 | 0.1 |
| Any antibiotic | 2962 | 41 | 1.4 | 1.0 | 1.9 | 2960 | 57 | 1.9 | 1.5 | 2.5 |
| **Overall/subject** | | | | | | | | | | |
| Any | 1513 | 137 | 9.1 | 7.7 | 10.6 | 1514 | 174 | 11.5 | 9.9 | 13.2 |
| Any antipyretic | 1513 | 20 | 1.3 | 0.8 | 2.0 | 1514 | 32 | 2.1 | 1.5 | 3.0 |
| Prophylactic antipyretic | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1513 | 36 | 2.4 | 1.7 | 3.3 | 1514 | 57 | 3.8 | 2.9 | 4.9 |

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

## Table 243 Incidence of concomitant medication within the 8-day (Days 0-7) post vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 153 | 10 | 6.5 | 3.2 | 11.7 | 153 | 9 | 5.9 | 2.7 | 10.9 |
| Any antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| Prophylactic antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| Any antibiotic | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| **Dose 2** | | | | | | | | | | |
| Any | 150 | 11 | 7.3 | 3.7 | 12.7 | 151 | 8 | 5.3 | 2.3 | 10.2 |
| Any antipyretic | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 2 | 1.3 | 0.2 | 4.7 |
| Prophylactic antipyretic | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Any antibiotic | 150 | 3 | 2.0 | 0.4 | 5.7 | 151 | 4 | 2.6 | 0.7 | 6.6 |
| **Overall/dose** | | | | | | | | | | |
| Any | 303 | 21 | 6.9 | 4.3 | 10.4 | 304 | 17 | 5.6 | 3.3 | 8.8 |
| Any antipyretic | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Prophylactic antipyretic | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| Any antibiotic | 303 | 9 | 3.0 | 1.4 | 5.6 | 304 | 6 | 2.0 | 0.7 | 4.2 |
| **Overall/subject** | | | | | | | | | | |
| Any | 153 | 21 | 13.7 | 8.7 | 20.2 | 153 | 17 | 11.1 | 6.6 | 17.2 |
| Any antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Prophylactic antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| Any antibiotic | 153 | 9 | 5.9 | 2.7 | 10.9 | 153 | 6 | 3.9 | 1.5 | 8.3 |

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

## Table 244 Incidence of concomitant medication within the 8-day (Days 0-7) post vaccination period (Total vaccinated cohort)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 1666 | 83 | 5.0 | 4.0 | 6.1 | 1667 | 118 | 7.1 | 5.9 | 8.4 |
| Any antipyretic | 1666 | 9 | 0.5 | 0.2 | 1.0 | 1667 | 20 | 1.2 | 0.7 | 1.8 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 24 | 1.4 | 0.9 | 2.1 | 1667 | 26 | 1.6 | 1.0 | 2.3 |
| **Dose 2** | | | | | | | | | | |
| Any | 1599 | 95 | 5.9 | 4.8 | 7.2 | 1597 | 88 | 5.5 | 4.4 | 6.7 |
| Any antipyretic | 1599 | 12 | 0.8 | 0.4 | 1.3 | 1597 | 16 | 1.0 | 0.6 | 1.6 |
| Prophylactic antipyretic | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1599 | 26 | 1.6 | 1.1 | 2.4 | 1597 | 37 | 2.3 | 1.6 | 3.2 |
| **Overall/dose** | | | | | | | | | | |
| Any | 3265 | 178 | 5.5 | 4.7 | 6.3 | 3264 | 206 | 6.3 | 5.5 | 7.2 |
| Any antipyretic | 3265 | 21 | 0.6 | 0.4 | 1.0 | 3264 | 36 | 1.1 | 0.8 | 1.5 |
| Prophylactic antipyretic | 3265 | 0 | 0.0 | 0.0 | 0.1 | 3264 | 0 | 0.0 | 0.0 | 0.1 |
| Any antibiotic | 3265 | 50 | 1.5 | 1.1 | 2.0 | 3264 | 63 | 1.9 | 1.5 | 2.5 |
| **Overall/subject** | | | | | | | | | | |
| Any | 1666 | 158 | 9.5 | 8.1 | 11.0 | 1667 | 191 | 11.5 | 10.0 | 13.1 |
| Any antipyretic | 1666 | 20 | 1.2 | 0.7 | 1.8 | 1667 | 34 | 2.0 | 1.4 | 2.8 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 45 | 2.7 | 2.0 | 3.6 | 1667 | 63 | 3.8 | 2.9 | 4.8 |

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

## Table 245 Incidence of concomitant medication during the entire study period (Total vaccinated cohort)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 1666 | 222 | 13.3 | 11.7 | 15.1 | 1667 | 287 | 17.2 | 15.4 | 19.1 |
| Any antipyretic | 1666 | 30 | 1.8 | 1.2 | 2.6 | 1667 | 48 | 2.9 | 2.1 | 3.8 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 78 | 4.7 | 3.7 | 5.8 | 1667 | 95 | 5.7 | 4.6 | 6.9 |
| **Dose 2** | | | | | | | | | | |
| Any | 1599 | 457 | 28.6 | 26.4 | 30.9 | 1597 | 485 | 30.4 | 28.1 | 32.7 |
| Any antipyretic | 1599 | 96 | 6.0 | 4.9 | 7.3 | 1597 | 105 | 6.6 | 5.4 | 7.9 |
| Prophylactic antipyretic | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1599 | 263 | 16.4 | 14.7 | 18.4 | 1597 | 311 | 19.5 | 17.6 | 21.5 |
| **Overall/dose** | | | | | | | | | | |
| Any | 3562 | 679 | 19.1 | 17.8 | 20.4 | 3562 | 772 | 21.7 | 20.3 | 23.1 |
| Any antipyretic | 3562 | 126 | 3.5 | 3.0 | 4.2 | 3562 | 153 | 4.3 | 3.7 | 5.0 |
| Prophylactic antipyretic | 3562 | 0 | 0.0 | 0.0 | 0.1 | 3562 | 0 | 0.0 | 0.0 | 0.1 |
| Any antibiotic | 3562 | 341 | 9.6 | 8.6 | 10.6 | 3562 | 406 | 11.4 | 10.4 | 12.5 |
| **Overall/subject** | | | | | | | | | | |
| Any | 1666 | 576 | 34.6 | 32.3 | 36.9 | 1667 | 644 | 38.6 | 36.3 | 41.0 |
| Any antipyretic | 1666 | 121 | 7.3 | 6.1 | 8.6 | 1667 | 144 | 8.6 | 7.3 | 10.1 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 310 | 18.6 | 16.8 | 20.6 | 1667 | 375 | 22.5 | 20.5 | 24.6 |

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

# 12. REFERENCES (CONTENTS OF MAJOR REFERENCES)

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# 13. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Project Statistician: [redacted]

Lead Statistician Rotavirus Vaccine
and Manager – Biostatistics: [redacted]

Global Study Manager: [redacted]

Central Safety Physician: [redacted]

Clinical Development Manager (CDM): [redacted]

Regulatory Affairs representative: [redacted]

Lead CDM: [redacted]

## 14.2. CIOMS reports

*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 |
| Randomisation list (patient identification and treatment assigned) | 16.1.7 |
| Audit certificates (if available) | 16.1.8 |
| Documentation of statistical methods | 16.1.9 |
| Documentation of inter-laboratory standardisation 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)<br>CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events | 16.3<br>16.3.1 |

# Sponsor Information

# Sponsor Information Sheet

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of document** | 13 June 2011 |
| **Version of document** | 13.1 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |

## 1. Country

China

## 2. Co-ordinating Investigator

[redacted]

[redacted] China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

## 3. Medical Monitor

[redacted]

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9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

## 4. Study Monitor

[redacted]

GlaxoSmithKline (China) Investment Co., Ltd.
9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

**Back up:**

[redacted]

GlaxoSmithKline (China) Investment Co., Ltd.
9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

**5. Study Contact for Reporting of a Serious Adverse Event**

Study Contact for Reporting SAEs (China)

[redacted]

GlaxoSmithKline (China) Investment Co., Ltd.
9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

Back-up Study Contact for Reporting SAEs (Belgium)

GSK Biologicals Clinical Safety Physician
Fax: [redacted] or [redacted]
24/24 hour and 7/7 day availability

**6. Study Contact for Emergency Code Break**

Mobile phones for 7/7 day availability:
Outside US/Canada:
[redacted] (GSK Biologicals Central Safety Physician)
Back-up mobile phone contact (all countries): [redacted]

**7. Study Centres**

[redacted] China

[redacted] China

[redacted] China

[redacted] China.

# Protocol and Protocol Amendments

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113808 (ROTA-075)
Amendment 2

**Clinical Study Protocol**
Sponsor:
**GlaxoSmithKline Biologicals**
Rue de l'Institut 89,1330 Rixensart, Belgium

| | |
|---|---|
| **Primary Study vaccine** | Liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine (444563) |
| **Other Study vaccines** | • GSK Biologicals' Placebo for liquid HRV vaccine.<br>• GSK Biologicals' Diphtheria-tetanus- acellular pertussis vaccine (DTPa).<br>• Institute of Medical Biology Chinese Academy of Medical Sciences' Oral poliovirus vaccine (OPV). |
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **Investigational New Drug (IND) number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Title** | Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Co-ordinating author** | [redacted] Scientific Writer |
| **Contributing authors** | • [redacted] Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA<br>• [redacted] MD., PhD., Senior Manager, GCDC, USA<br>• [redacted] Project Statistician, CDOC-B |

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113808 (ROTA-075)
Amendment 2

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **Investigational New Drug (IND) number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
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| **Contributing authors** | • [redacted] Global Study Manager, GCRD<br>• [redacted] Manager Biometrics, CDOC-B<br>• [redacted] Safety Scientist, SERM<br>• [redacted] Manager, R&D Laboratory<br>• [redacted] ***Clinical Immunology representative***<br>• [redacted] Clinical Data Coordinator, CDOC-B<br>• [redacted] [redacted] GSK Biologicals – China and Hong Kong<br>• [redacted] Head of Clinical R&D, China<br>• [redacted] Senior Medical Affairs Manager, China |

***GSK Biologicals' Protocol DS v 13.1***

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113808 (ROTA-075)
Amendment 2

# Protocol Amendment 2 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010. |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted]<br>Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | _____ |
| **Date** | _____ |

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# Protocol Amendment 2 Rationale

| **Amendment number:** Amendment 2 |
|---|
| **Rationale/background for changes:** Based on the preliminary review of GE episodes reported to date prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seems lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up needs to be extended till April 2012 (i.e. end of RV season in China).<br>• Section 1.1: Background<br>• Synopsis and Section 1.2: Rationale for the study and study design<br>• Synopsis and Section 3: Study Design Overview<br>• Section 4.1: Number of subjects/centres<br>• Section 5.5: Outline of study procedures<br>• Section 5.6.3.12: Recording GE occurring throughout the study period in a GE diary card<br>• Section 5.6.3.13: Collection of stool samples in case the child develops GE<br>• Section 5.6.3.14: Return of diary cards and GE diary cards<br>• Section 5.6.3.15: Diary card and GE diary card transcription by investigator<br>• Section 5.6.4 Procedures during Efficacy follow-up (Visit 6)<br>• Section 5.6.5 Procedures during Efficacy follow-up (Visit 7)<br>• Section 5.7.2: Biological samples<br>• Section 5.7.3: Laboratory Assays<br>• Section 6.7.2: Time window for recording concomitant medication/vaccination in the eCRF<br>• Section 8.3.1: Time period for detecting and recording adverse events, serious adverse events<br>• Synopsis and Section 10.1: Primary endpoint<br>• Synopsis and Section 10.2: Secondary endpoints<br>• Section 10.3: Estimated sample size<br>• Section 10.5: Derived and transformed data<br>• Section 10.6.1: Sequence of analyses<br>• Section 10.7.2: Analysis of efficacy<br>• Section 10.7.4: Analysis of safety |

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# Protocol Amendment 2 Investigator Agreement

**I agree:**

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (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.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- 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 updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | |
| **Signature** | |
| **Date** | |



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# SYNOPSIS

**Detailed Title**

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

**Indication**

Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

**Rationale for the study and study design**

– **Rationale for the study and study design**

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of file for licensure in China.

The primary objective of this study is to evaluate the efficacy of the liquid HRV vaccine to prevent severe RV GE during the efficacy follow-up period. There will be an efficacy follow-up starting 2 weeks after the second dose of study vaccination till ***April 2012 (i.e. end of RV season in China)***. **Amended: 05 August 2011.**

GSK Biologicals also intends to submit immunogenicity and reactogenicity data of the liquid HRV vaccine and co-administered routine vaccines to the regulatory authorities. In order to assess the immunogenicity of the study vaccines, two immunogenicity sub-cohorts are planned to be enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo will be assessed in the first sub-cohort (N = 600). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 will be assessed in the second sub-cohort (N = 300). Reactogenicity of the liquid HRV vaccine/Placebo will be assessed in the whole cohort except immunogenicity second sub-cohort.

– **Rationale for the use of placebo**

As per recommendations of the regulatory authorities in China, it is suggested to include a control group in vaccine registration trials. As it is not feasible to find an appropriate active control for the liquid HRV vaccine, it was agreed to by the regulatory authorities and GSK Biologicals to include placebo as a comparable control. The inclusion of placebo in this trial will allow the assessment of efficacy, safety and immunogenicity of the liquid HRV vaccine as compared to the placebo.

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**Objectives**

**Primary**

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy is at least 10%.

**Secondary**

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid

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HRV vaccine/placebo and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6 when co-administered with the routine childhood vaccines
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

**Study design**

- Experimental design: Phase III, double blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: ***The subjects will be followed until April 2012 (i.e. end of RV season in China).*** The

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intended duration of the study, per subject, will ***not exceed a maximum of 21 months***. The study will have a single epoch as follows. **Amended: 05 August 2011.**

– Primary: Primary starting Visit 1 (Day 0) and ending ***Visit 7 (April 2012 i.e. end of RV season in China)***. **Amended: 05 August 2011.**

Synopsis Table 1 presents study groups and epoch foreseen in the study.

**Synopsis Table 1 Study groups and epochs foreseen in the study**

| Group identifier | Number of subjects | Age (Min/Max) | Epochs |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 –16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedule: Two oral doses of the liquid HRV vaccine or placebo will be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.

  Subjects in each group will receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study must be documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (N = 1625)
  - Group Placebo (N = 1625)

The treatment groups for the study are presented in Synopsis Table 2.

**Synopsis Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine will be given concomitantly with liquid HRV vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

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- Treatment allocation: Randomised with balanced allocation (1:1).
- Blinding: Double-blind study.

Synopsis Table 3 presents blinding of study epoch.

**Synopsis Table 3 Blinding of study epochs**

| Study Epoch | Blinding |
|---|---|
| Primary | double-blind |

- Blood Sampling: Blood samples will be collected from two sub-cohorts of subjects.
  - Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).
  - Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) of liquid HRV vaccine/placebo after each dose, using diary cards (applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (applicable only for subjects in the immunogenicity sub-cohort 2).
- Unsolicited AEs will be followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV

vaccine/placebo.

- Recording of SAEs throughout the study period for all subjects.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.*** **Amended: 05 August 2011.**
- Active follow-up for occurrence of GE* episodes will be conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE is defined as diarrhoea with or without vomiting.
- For each GE episode occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after GE symptoms begin.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.*** **Amended: 05 August 2011.**
- ***All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).*** **Amended: 05 August 2011.**
- ***The additional informed consent will be taken for the extended follow-up.*** **Amended: 05 August 2011.**
- Type of study: self-contained
- Data collection: eCRF.
- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ***study conclusion***,

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an annex report will present ***all*** data up to ***study conclusion***. **Amended: 05 August 2011.**

**Number of subjects** Target enrolment will be 3250 eligible subjects. (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

**Endpoint**

**Primary**

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).**Amended: 05 August 2011.**

**Secondary**

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***). **Amended: 05 August 2011.**

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects).*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at

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Visit 3 and seropositivity rate at Visit 6.

– Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- Anti-rotavirus IgA antibody concentrations.
  – Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  – Serum anti-rotavirus IgA antibody concentrations expressed as GMC at Visit 3 and at Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  – Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  – Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  – Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2

of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ATP** | According-To-Protocol |
| **$CCID_{50}$** | Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells) |
| **CI** | Confidence Interval |
| **DMEM** | Dulbecco's Modified Eagle Medium |
| **DTPa** | Diphtheria, Tetanus, acellular Pertussis vaccine |
| **eCRF** | electronic Case Report Form |
| **$ED_{50}$** | Estimated dose 50% |
| **EL.U/mL** | ELISA Units per Millilitre |
| **ELISA** | Enzyme Linked Immunosorbent Assay |
| **EPI** | Expanded Program of Immunisation |
| **FHA** | Filamentous Haemagglutinin |
| **GCP** | Good Clinical Practice |
| **GE** | Gastroenteritis |
| **GMC** | Geometric Mean Concentration |
| **GSK** | GlaxoSmithKline |
| **GSM** | Global Study Manager |
| **HRV** | Human Rotavirus |
| **IB** | Investigator Brochure |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IgA** | Immunoglobulin A |
| **IM** | Intramuscular |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **IS** | Intussusception |
| **IU/mL** | International Units per Millilitre |
| **LAR** | Legally Acceptable Representative |
| **LSC** | Local Study Contact |
| **MedDRA** | Medical Dictionary for Regulatory Activities |

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| | |
|---|---|
| **Mg** | Milligram |
| **mL** | Millilitre |
| **MMWR** | Morbidity and Mortality Weekly Report |
| ***NIFDC*** | ***National Institute for Food and Drug Control*** |
| **O** | Oral |
| **OPV** | Oral Poliovirus vaccine |
| **PCR** | Polymerase Chain Reaction |
| **PRN** | Pertactin |
| **PT** | Pertussis toxid |
| **RV** | Rotavirus |
| **SAE** | Serious Adverse Event |
| **SAS** | Statistical Analysis System |
| **SBIR** | Internet Randomisation tool |
| **SDV** | Source Document Verification |
| **SPM** | Study Procedures Manual |
| **U/mL** | Units per Millilitre |
| **UA** | Upper Arm |
| **UMV** | Universal Mass Vaccination |
| **VE** | Vaccine Efficacy |
| **WHO** | World Health Organisation |

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# GLOSSARY OF TERMS

| | |
|---|---|
| **According-To-Protocol cohort:** | This cohort will include all subjects enrolled in the study who meet the criteria defined in the protocol for the considered analysis (Efficacy, immunogenicity, reactogenicity and safety). |
| **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.<br><br>An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. |
| **Blinding:** | A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event (SAE). |
| **Child in care:** | A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian. |
| **Diarrhoea:** | Passage of three or more looser than normal stools within a day. |
| **Eligible:** | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |

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| | |
|---|---|
| **Epoch:** | An epoch is a well defined part of a protocol that covers a set of consecutive time-points. Generally, an epoch is self-contained and allows to perform a data analysis to address some of the trial objectives (e.g. primary, booster, yearly follow-ups). |
| **eTrack:** | GSK's tracking tool for clinical trials. |
| **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 6.7.1 and 10.4 for details on criteria for evaluability). |
| **Gastroenteritis:** | Diarrhoea with or without vomiting. |
| **Investigational vaccine/product:**<br><br>**(Synonym of Investigational Medicinal 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. |
| **Legally Acceptable Representative:** | ICH GCP defines Legally Accepted Representative (LAR) as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. |
| **Randomisation:** | Process of random attribution of treatment to subjects in order to reduce bias of selection. |
| **Serious adverse event:** | 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 event 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. |
| **Severe rotavirus gastroenteritis:** | An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system). |

| | |
|---|---|
| **Site Monitor:** | An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites. |
| **Solicited adverse event:** | AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject's parents/ LARs or an observer during a specified post-vaccination follow-up period. |
| **Sub-cohort:** | A group of subjects for whom specific data are collected compared to other subjects. |
| **Subject:** | Term used throughout the protocol to denote an individual whose parents/LARs have been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Total vaccinated cohort:** | The total vaccinated cohort will include all subjects with at least one vaccine administration documented. A safety analysis based on the total vaccinated cohort will include all vaccinated subjects. An immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects for whom immunogenicity data are available. An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available. |
| **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:** | A number identifying a treatment to a subject, according to the study randomisation or treatment allocation. |
| **Unsolicited adverse event:** | Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE. |
| **Vomiting:** | One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day. |

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# TRADEMARKS

The following trademarks are used in the present protocol.

**Note:** In the body of the Protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ™.

| Trademarks of the GlaxoSmithKline group of companies | Generic description |
|---|---|
| Rotarix™ | Human rotavirus vaccine |
| Infanrix™ | Combined diphtheria-tetanus-acellular pertussis (DTPa) vaccine |

| Trademarks not owned by the GlaxoSmithKline group of companies | Generic description |
|---|---|
| OPV (Institute of Medical Biology Chinese Academy of Medical Sciences') | Poliomyelitis (live) Vaccine (Monkey Kidney Cell), Oral |

# 1. INTRODUCTION

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) among young children aged <5 years. A recent review estimated that RV is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year where the majority of the deaths occur in the developing countries in Asia and Africa [WHO, 2007]. In developed countries, RV infection rarely results in death but RV remains the most common cause of hospitalisation for GE in children and leads to major medical and societal costs [Glass, 1996].

Hospital-based surveillance performed in Asia indicates that 20 to 50% of hospitalisations for diarrhoea among children less than five years of age are associated with RV infection and the morbidity and mortality may be much higher than in previously estimated RV infections. RV infections occur in all children during the first few years of life, suggesting that the virus is not primarily transmitted through the oro-faecal route. Improved hygiene and sanitation therefore cannot alone result in decreased RV infections. RV infections frequently occur with vomiting, which can result in discontinuation of oral rehydration therapy. Although first infections can lead to disease that ranges from mild GE to severe or fatal diarrhoea with dehydration, they also can induce immunity against severe disease after reinfection. Based on these data, vaccines have been identified as the best current strategy to decrease the burden associated with severe and fatal RV diarrhoea [Kang, 2006].

China has the second largest birth cohort in the world and the second highest number of deaths due to RV infection. In China, RV is the most common cause of diarrhoea and an economic burden for the parents. Approximately 27, 000 RV associated deaths occur each year and 32% - 50% of the hospitalised diarrhoea are associated with an RV infection [Naghipour, 2008; Wang, 2009].

In a hospital based study in Shanghai, more than 80% of the children with RV infections were aged less than 2 years [Xu, 2008]. Since RV is the most important cause of acute GE, this large disease burden of RV GE in children points towards vaccination as an effective preventive measure. In China, introduction of a RV vaccine would most likely be beneficial for children and a significant proportion of the diarrhoeal disease burden might be prevented in the near future [Liu, 2006].

GlaxoSmithKline (GSK) Biologicals therefore has developed a human rotavirus (HRV) vaccine to meet this health need. GSK Biologicals' HRV vaccine is a monovalent vaccine based on a HRV strain 89-12 belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old infant with mild RV diarrhoea in Cincinnati, United States. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilised HRV vaccine containing RIX4414 cloned from 89-12 at passage 43 for oral administration after reconstitution with buffer. The parent 89-12 vaccine was well-tolerated, immunogenic and effective in preventing RV GE among vaccinated infants during a trial in the United States [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002].

GSK Biologicals' lyophilised HRV vaccine has been extensively tested in clinical studies conducted in infants from Europe, North America, Latin America and the Caribbean, Asia and Africa. This vaccine was well-tolerated, immunogenic and efficacious against RV disease of any severity in infants [Vesikari, 2004; Vesikari, 2006]. Efficacy results from a subset (20,169 subjects) from the Latin American safety study followed for 9 to 10 months after Dose 2 of the vaccine demonstrated a high protection rate (85%) against severe RV GE and this rate reached 100% protection against the most severe RV GE (defined as GE with a Vesikari score of 19 or 20) [Ruiz Palacios, 2006]. Other large scale efficacy studies conducted in Europe confirmed the efficacy and cross-protection provided by the HRV vaccine [Vesikari, 2007].

## 1.1. Background

GSK Biologicals has also developed a liquid formulation of the HRV vaccine containing the same HRV strain (RIX4414), referred to as the "liquid HRV vaccine". Two doses of GSK Biologicals' liquid HRV vaccine have been evaluated and were as immunogenic as the lyophilised formulation in terms of anti-rotavirus Immunoglobulin A (IgA) antibody response. When co-administered with routine childhood vaccines including oral poliovirus vaccine (OPV), the liquid HRV vaccine was found to be immunogenic and similar to the lyophilised HRV vaccine. The liquid HRV vaccine is currently registered in ***at least 77 countries*** worldwide including Mexico, Brazil, Australia and the European Union. **Amended: 05 August 2011**

Please refer to the current Investigator Brochure for a review of the pre-clinical and clinical studies, and the potential risks and benefits of liquid HRV vaccine.

## 1.2. Rationale for the study and study design

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of file for licensure in China.

The primary objective of this study is to evaluate the efficacy of the liquid HRV vaccine to prevent severe RV GE during the efficacy follow-up period. There will be an efficacy follow-up starting 2 weeks after the second dose of study vaccination till ***April 2012 (i.e. end of RV season in China).*** **Amended: 05 August 2011.**

GSK Biologicals also intends to submit immunogenicity and reactogenicity data of the liquid HRV vaccine and co-administered routine vaccines to the regulatory authorities. In order to assess the immunogenicity of the study vaccines, two immunogenicity sub-cohorts are planned to be enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo will be assessed in the first sub-cohort (N = 600). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 will be assessed in the second sub-cohort (N = 300). Reactogenicity of the liquid HRV vaccine/Placebo will be assessed in the whole cohort except immunogenicity second sub-cohort.

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### 1.2.1. Rationale for the use of placebo

As per recommendations of the regulatory authorities in China, it is suggested to include a control group in vaccine registration trials. As it is not feasible to find an appropriate active control for the liquid HRV vaccine, it was agreed to by the regulatory authorities and GSK Biologicals to include placebo as a comparable control. The inclusion of placebo in this trial will allow the assessment of efficacy, safety and immunogenicity of the liquid HRV vaccine as compared to the placebo.

# 2. OBJECTIVES

## 2.1. Primary objective

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy is at least 10%.

Refer to Section 10.1 for the definition of the primary endpoint.

## 2.2. Secondary objectives

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

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*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at visit 6 when co-administered with the routine childhood vaccines
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

Refer to Section 10.2 for the definition of the secondary endpoints.

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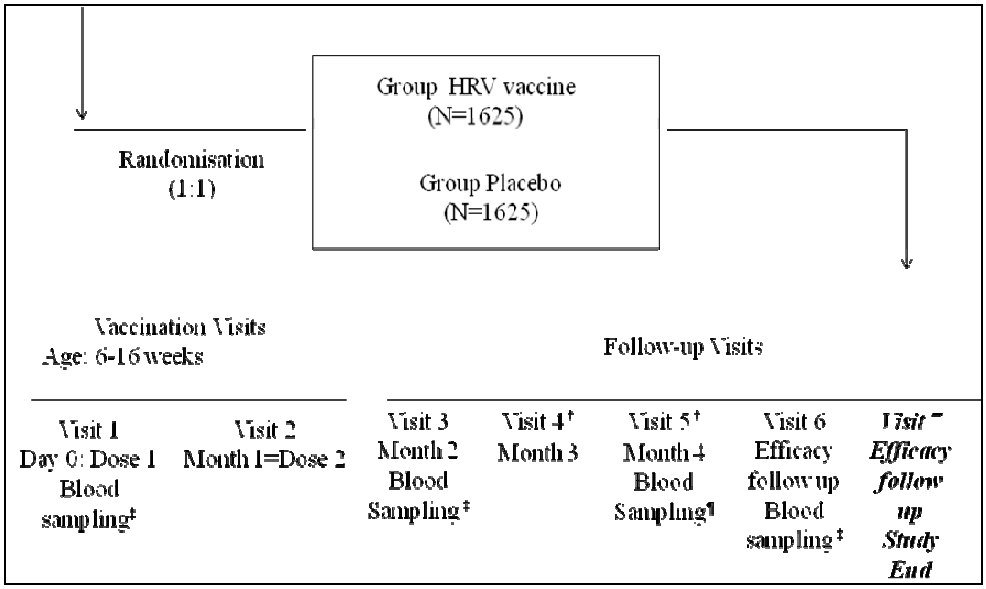
# 3. STUDY DESIGN OVERVIEW

The study design for all subjects is as follows: **Amended: 05 August 2011.**




N: Number of subjects planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort2.
‡Blood will be drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood will be drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 will receive a dose of OPV at Visit 1, Visit 2 and Visit 3; and will receive a dose of DTPa at Visit 2, Visit 3 and Visit 4

- Experimental design: Phase III, double-blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.

- Duration of the study: ***The subjects will be followed until April 2012 (i.e. end of RV season in China).*** The intended duration of the study, per subject, will ***not exceed a maximum of 21 months***. The study will have a single epoch as follows. **Amended: 05 August 2011.**

  – Primary: Primary starting Visit 1 (Day 0) and ending Visit *7* ***(April 2012 i.e. end of RV season in China)***. **Amended: 05 August 2011.**

Table 1 presents the study groups and the epoch foreseen in the study.

**Table 1 Study groups and epochs foreseen in the study**

| Study group | Number of subjects | Age in weeks (MIN/Max) | Epoch |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 – 16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

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- Control: placebo control.
- Vaccination schedules: Two oral doses of the liquid HRV vaccine or placebo will be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.
  - Subjects in each group will receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study must be documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (N = 1625)
  - Group Placebo (N = 1625)

The treatment groups for the study are presented in Table 2.

**Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine will be given concomitantly with liquid HRV Vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

- Treatment allocation: Randomised with balanced allocation (1:1).

Refer to Section 5.2 for a detailed description of the randomisation method.

- Blinding**:** Double-blind study.

Refer to Section 5.3 for details of blinding procedure.

Table 3 presents the blinding of the study epoch.

**Table 3 Blinding of study epochs**

| Study Epochs | Blinding |
|---|---|
| Primary | double-blind |

Refer to Section 8.6 for details on when unblinding will be done.

- Blood Sampling: Blood samples will be collected from two sub-cohorts of subjects.

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).

- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).

- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) of liquid HRV vaccine/placebo after each dose, using diary cards (applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).

- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (applicable only for subjects in the immunogenicity sub-cohort 2).

- Unsolicited AEs will be followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV vaccine/placebo.

- Recording of SAEs throughout the study period for all subjects.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.*** **Amended: 05 August 2011.**

- Active follow-up for occurrence of GE* episodes will be conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE is defined as diarrhoea with or without vomiting.

- For each GE episode occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after GE symptoms begin.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.*** **Amended: 05 August 2011.**

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- ***All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).*** **Amended: 05 August 2011.**

- ***The additional informed consent will be taken for the extended follow-up.*** **Amended: 05 August 2011.**

- Type of study: self-contained.

- Data collection: eCRF .

- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ***study conclusion***, an annex report will present ***all*** data up to ***study conclusion***. **Amended: 05 August 2011.**

# 4. STUDY COHORT

## 4.1. Number of subjects/centres

Target enrolment will be 3250 eligible subjects. (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

Refer to Section 10.3 for a detailed description of the criteria used in the estimation of the sample size.

Table 4 presents the sub-cohorts in the study.

**Table 4 Sub-cohorts**

| Sub-cohort name | Description | Estimated number of subjects |
|---|---|---|
| Immunogenicity Sub-cohort 1 | To assess the immunogenicity of the liquid HRV vaccine/placebo.<br>To assess the reactogenicity of the liquid HRV vaccine/placebo.<br>To assess the safety (unsolicited AEs and SAEs) of the liquid HRV/placebo | 600 |
| Immunogenicity Sub-cohort 2 | To assess the immunogenicity of the liquid HRV vaccine/placebo as well as the routine childhood vaccines (i.e. OPV and DTPa).<br>To assess the reactogenicity of OPV and DTPa only at Visit 1 and Visit 2.<br>To assess the safety (unsolicited AEs and SAEs) of the liquid HRV/placebo<br>Reactogenicity of the liquid HRV vaccine/placebo will not be assessed | 300 |

Overview of the recruitment plan

- Enrolment will be terminated when 3250 eligible subjects have been enrolled.
- All enrolled subjects will be followed for efficacy and safety.
- The intended duration of the study, per subject, will ***not exceed a maximum of 21 months***. **Amended: 05 August 2011.**
- The recruitment will be monitored by Internet Randomisation tool (SBIR).

## 4.2. Inclusion criteria for enrolment

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who the investigator believes that their parents/Legally Acceptable Representatives (LARs) can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parents/LARs of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of 36 to 42 weeks inclusive.

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## 4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If **ANY** exclusion criterion applies, the subject must not be included in the study:

- Child in care.

  Refer to the GLOSSARY OF TERMS for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone 0.5 mg/kg/day, or equivalent, inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccines and ending 14 days after.of the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.
- 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).
- Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for Intussusception (IS).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness.
- History of confirmed RV GE.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature (37.1°C on axillary setting as defined by the Chinese authorities.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).
- GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).

- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

In addition to the criteria mentioned above, the following criteria will be applicable to all subjects in the immunogenicity sub-cohort 2:

- History of diphtheria, tetanus and pertussis disease.
- History of seizures or progressive neurological disease.
- Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

# 5. CONDUCT OF THE STUDY

## 5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject's parents/LARs informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written informed consent must be obtained from each subject's parent(s)/LAR(s), prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to 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 local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

## 5.2. Subject identification and randomisation of treatment

The target will be to enrol 3250 eligible subjects to be randomly assigned to two study groups in a balanced (1:1) ratio (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

### 5.2.1. 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.

### 5.2.2. Randomisation of treatment

#### 5.2.2.1. Randomisation of supplies

The randomisation will be performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS® ) (Cary, NC, USA) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, a 6%-over-randomisation of supplies will be prepared.

The vaccine doses will be distributed to the study centres while respecting the randomisation block size.

#### 5.2.2.2. Treatment allocation to the subject

The treatment allocation at the investigator site will be performed using SBIR. The treatment numbers will be allocated by kit. The randomisation algorithm will use a minimisation procedure accounting for centre.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

After having checked the eligibility of the subject and obtaining the ICF, the site staff in charge of the vaccination will access SBIR. Upon providing the subject identification

number, the randomisation system will use the minimisation algorithm to determine the treatment number to be used for the subject. Each treatment number must be recorded in the eCRF on the Vaccine Administration screen.

### 5.2.3. Randomisation of subjects to assay sub-cohorts

Randomisation for all the sub-cohorts will be done in parallel Blood samples will be collected from both the sub-cohorts of subjects:

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).
- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300).

## 5.3. Method of blinding

The study will be conducted in a double-blind manner with respect to the liquid HRV vaccine and placebo. The parents/LARs of the subjects, the study personnel and the investigator will be unaware of the study vaccine administered (liquid HRV vaccine/Placebo).

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 SAE.

If the final analysis will be done by an independent analysis centre in order to preserve blinding as much as possible, when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period, access to the individual treatment decode during the final analysis will be limited to the statistician and the database administrator to maintain double blinding until study end. This will allow unbiased evaluation of the study vaccine.

The serological data, which would lead to the unblinding of the treatment groups, will not be available during the course of the study to any investigator or any person involved in the clinical conduct of the study (including data cleaning).

## 5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

### 5.4.1. Routine vaccinations

Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All other subjects will receive

routine childhood vaccinations according to the local immunisation practice. Administration of all routine childhood vaccinations since birth must be documented in the eCRF.

### 5.4.2. Follow-up of GE cases

Parents/LARs of all subjects will be instructed to collect a stool sample from the subject if the subject develops GE symptoms (defined as diarrhoea with or without vomiting) during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks). A GE stool sample should be collected as soon as possible after the illness begins. A second GE stool sample is to be collected if the first sample was insufficient. A stool sample should be collected for each GE episode. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes.

For each suspected GE episode occurring during the study period, a GE diary card should be completed by the parents/LARs daily until end of the GE symptoms. The completed diary cards should be returned to the investigator at the following study visit. The investigator will verify the returned completed GE diary cards and he or the study personnel will transcribe the information into the appropriate sections of the eCRF, in English.

### 5.4.3. Standard of Care

All subjects will undergo a general physical examination. If during the study, the investigator discovers any underlying medical condition, the subject will be referred to the local healthcare system.

## 5.5. Outline of study procedures

Table 5 presents the list of study procedures.

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**Table 5 List of study procedures (Amended: 05 August 2011)**

| **Age** | **6 to 16 weeks** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Epoch** | **Primary** | | | | | **Efficacy follow-up** | |
| **Type of contact** | **visit 1** | **visit 2** | **visit 3** | **visit 4 *** | **visit 5 *** | **visit 6** | ***Visit 7*** |
| **Time-points** | **days 0** | **months 1** | **months 2** | **months 3** | **months 4** | ***years* 1 of age** | ***April 2012[β]*** |
| **Sampling time-points** | **Pre-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Efficacy follow up** | ***Efficacy follow up*** |
| Informed consent | ● | | | | | | |
| ***Re-consenting for Visit 7 follow-up*** | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | O | O | O | O | O | O |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approxi-mately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 2) | ● (Approxima-tely 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+DTPa) | ● (OPV+DTPa) | ● (DTPa) | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of ***unsolicited AEs*** within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |

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| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | visit 1 | visit 2 | visit 3 | visit 4 * | visit 5 * | visit 6 | *Visit 7* |
| Time-points | days 0 | months 1 | months 2 | months 3 | months 4 | *years* 1 of age | *April 2012*[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | *Efficacy follow up* |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | O | O | O | O | O | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
***[β]i.e. end of the RV season in China. Amended: 05 August 2011***

Table 6 presents the intervals between study visits.

**Table 6 Intervals between study visits (Amended: 05 August 2011)**

| Interval | Optimal length of interval [1] | Maximum interval allowed [2] |
|---|---|---|
| 1 (Visit 1)→(Visit 2) | 30-48 days | 21-48 days |
| 2 ((Visit 2)→(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3)→(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | ***1 year of age± 2 weeks[γ]*** | ***1 year of age ± 30 days*** |
| ***6 (Visit 6) → (Visit 7)*** | ***01 April 2012 to 30 April 2012[γ]*** | ***01 April 2012 to 31 May 2012*** |

[1]. Whenever possible the investigator should arrange study visits within this interval
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they make the study visit outside this interval
***[γ]It is a defined time point for follow up visit in a range and not an interval. Amended: 05 August 2011***
Note: The date of the previous visit serves as the reference date for intervals between study visits. Refer to section 3 for details on the study visits applicable to the subjects in the study.

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## 5.6. Detailed description of study procedures

### 5.6.1. Procedures prior to study participation

#### 5.6.1.1. Informed consent

Before performing any other study procedure, the signed/thumb printed informed consent of the subject's parents/LARs needs to be obtained. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

### 5.6.2. Procedures prior to the first vaccination

#### 5.6.2.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

#### 5.6.2.2. Collect demographic data

Record demographic data such as date of birth, gender, race in the subject's eCRF.

#### 5.6.2.3. Collect gestational age

Gestational age of the subject needs to be collected and recorded in the eCRF.

#### 5.6.2.4. Medical history

Perform a history-directed medical examination and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

#### 5.6.2.5. Physical examination

Perform a physical examination of the subject, including assessment of body temperature, height and weight. Collected information needs to be recorded in the eCRF.

#### 5.6.2.6. Blood sampling for antibody determination

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

During Visit 1 a volume of approximately 3 mL of whole blood to get a serum volume of 1.5 mL will be drawn from subjects belonging to immunogenicity sub-cohort 1 and a volume of approximately 4.5 mL of whole blood to get a serum volume of 2 mL will be

drawn from subjects belonging to immunogenicity sub-cohort 2 included in the immunogenicity sub-cohort for each analysis of humoral immune response at each pre-defined time-point. After centrifugation, serum samples should be kept at –20°C until shipment.

### 5.6.3. Procedures during the primary epoch

#### 5.6.3.1. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant vaccination must be recorded in the eCRF as described in Section 6.7. Refer also to Section 6.7for details on the medication/vaccination forbidden and/or allowed during the study.

At each study visit subsequent to the first vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition listed in Section 6.8. If it is the case, the condition(s) must be recorded in the eCRF.

#### 5.6.3.2. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination are to be checked at Visit 1 and Visit 2. Refer to Section 6.5and 6.6.

#### 5.6.3.3. Pre-vaccination body temperature / Assess pre-vaccination body temperature

The axillary body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be axillary. If the subject has fever (Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.), the vaccination visit will be rescheduled within the interval for this visit (see Table 5).

#### 5.6.3.4. Randomisation

At the first vaccination visit, randomisation will occur as explained in Section 5.2.

#### 5.6.3.5. Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis

Information regarding previous vaccination of subjects with diphtheria, tetanus, pertussis and poliomyelitis needs to be recorded in eCRF.

#### 5.6.3.6. Blood sampling for antibody determination

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

A volume of approximately 3 mL of whole blood to get a serum volume of 1.5 mL will be drawn from subjects belonging immunogenicity sub-cohort 1 and 2 during Visit 3. During Visit 5, a volume of approximately 3 mL of blood get a serum volume of 1.5 mL will be drawn only from subjects in immunogenicity sub-cohort 2 included in the immunogenicity sub-cohort for each analysis of humoral immune response at each pre-defined time-point. After centrifugation, serum samples should be kept at –20°C until shipment.

#### 5.6.3.7. Treatment number assignment

At the first vaccination visit, the subject will be assigned a treatment number defining the treatment he/she will be receiving. The treatment number must be recorded in the eCRF at each vaccination visit.

#### 5.6.3.8. Vaccination

After completing the pre-requisite procedures prior to vaccination, one dose of study vaccine (liquid HRV vaccine) or placebo will be administered orally (refer to Section 6 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit. The subjects will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccines.

#### 5.6.3.9. Recording of co-administered vaccines in sub-cohort 2

The co-administered vaccines in sub-cohort 2 (OPV and DTPa vaccine) will be recorded as and when administered by the investigator in eCRF.

#### 5.6.3.10. Daily post-vaccination recording of solicited general adverse events after each dose of vaccines/ placebo given.

- Refer to Section 8.3 for procedures for the Investigator to record AEs and SAEs that are related to study participation or GSK concomitant medication/vaccination and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.

- The subjects' parents/LARs will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms parents/LARs perceive as serious.

- After each dose of liquid HRV vaccine/placebo, diary cards will be provided to the subjects parents/LARs to record body (axillary) temperature and any solicited general AEs daily (i.e. on the day of vaccination and during the next 7 days) occurring within 8 days of liquid HRV/ placebo vaccination. This procedure will be done for all subjects except for subjects in immunogenicity sub-cohort 2.

- After Dose 1 and Dose 2 of OPV, diary cards will be provided to the subjects parents/LARs to record body (axillary) temperature and any solicited general AEs daily (i.e. on the day of vaccination and during the next 7 days) occurring within 8 days of OPV vaccination. This procedure will be followed only for subjects in immunogenicity sub-cohort 2.

- After Dose 1 of DTPa vaccine, diary cards will be provided to the subjects parents/LARs to record body (axillary) temperature and any solicited local and general AEs daily (i.e. on the day of vaccination and during the next 7 days) occurring within 8 days of DTPa vaccination. This procedure will be followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.11. Recording of serious and non-serious adverse events

- Refer to Section 8.3 for procedures for the investigator to record AEs and SAEs that are related to study participation or GSK concomitant medication/vaccination and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.

- The subjects' parents/LARs will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

- At each visit, diary cards will be provided to the subjects' parents/LARs to record body (axillary) temperature and any SAEs occurring during visit intervals until the next visit. This procedure of recording serious AEs will be done throughout the study (after first vaccine dose till study end). The parents/LARs will be instructed to return the completed diary card to the Investigator at the next visit.

- Any non serious AEs occurring within 31 days (Day 0 – 30) post vaccination will be recorded by the investigator in eCRF.

#### 5.6.3.12. Recording GE occurring throughout the study period in a GE diary card

At each visit, GE diary cards will be provided to the subject's parents/LARs to record any GE episodes occurring after vaccination and during visit intervals. The GE diary card should be completed by the parents/LARs daily until end of the GE symptoms. The parents/LARs will be instructed to return the completed diary card to the Investigator at the next visit.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.13. Collection of stool samples in case the child develops GE

As specified in the List of Study Procedures in Section 5.5 (Table 5), Parents/LARs of all subjects will be instructed to collect a stool sample from the subject if the subject develops GE symptoms (defined as diarrhoea with or without vomiting) during the course of the study starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks). A GE stool sample should be collected as soon as possible after the illness begins. A second GE stool sample is to be collected if the first sample was insufficient. A stool sample should be collected for each GE episode. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Samples should be transferred rapidly to the investigator's laboratory or investigator's site (within 0 to 3 days).

Refer to the Module on Biospecimen Management in the SPM for general handling of stool samples.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.14. Return of diary cards and GE diary cards

The completed diary cards and GE diary cards will be collected and verified during discussion with the subject's parents/LARs at the subsequent visit. Any unreturned GE diary cards will be sought from the subject's parents/LARs through a convenient procedure.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.15. Diary card and GE diary card transcription by investigator

The investigator will transcribe the information collected from diary cards and GE diary cards into the eCRF in English.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

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### *5.6.4.* Procedures during Efficacy follow-up *(Visit 6)*

***For subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2:***

***The additional consent will be obtained from the subject's parents/LARs. Retrospective data on intercurrent medical condition, concomitant medication/vaccination, GE episodes and SAEs will also be collected.***

***For subjects who are returning for Visit 6 after the implementation of protocol amendment 2:***

Note that some of the procedures to be performed during the follow-up visits (such as physical examination, blood sampling, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of ***S***AEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11. ***For the participation in the extended follow-up till Visit 7, additional consent of subject's parents/LARs will be obtained.*** **Amended: 05 August 2011.**

#### 5.6.4.1. Blood sampling for antibody determination

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

A volume of approximately 3 mL of whole blood to get a serum volume of 1.5 mL will be drawn from subjects in immunogenicity sub-cohort 1 and 2 during Visit 6 included in the immunogenicity sub-cohort for each analysis of humoral immune response at each pre-defined time-point. After centrifugation, serum samples should be kept at –20°C until shipment.

### *5.6.5. Procedures during Efficacy follow-up (Visit 7)*

***Note that some of the procedures to be performed during the follow-up visits (such as physical examination, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of SAEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11.*** **Amended: 05 August 2011.**

#### 5.6.5.1. Study conclusion

The investigator will review all the data collected to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

At study conclusion, post-trial commercial vaccines will not be provided to the subjects.

## 5.7. Biological sample handling and analysis

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

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

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccines and its constituents or the disease under study to allow to achieve a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the subject's parent(s)/LAR(s).

Any human pharmacogenetic testing will require specific consent from the individual subject's parents/LARs and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendments.

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

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

### 5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals or GSK designated laboratory (such as a central laboratory), it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the According-To-Protocol (ATP) analysis (See Section 10.4 for the definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to the Module on Clinical Trial Supplies in the SPM.

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### 5.7.2. Biological samples

Table 7 presents the biological samples used in this study.

**Table 7 Biological samples (Amended: 05 August 2011)**

| Sample type | Quantity | Unit | Time-point | Sub-cohort Name* |
|---|---|---|---|---|
| Blood | Approximately 3 | ml | Schedule (Visit 1) days 0 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 4.5 | ml | Schedule (Visit 1) days 0 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) months 2 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) months 2 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 5) months 4 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) years 1 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) years 1 | Immunogenicity Sub-cohort 2 |
| Stool | NA | NA | Schedule From Visit 1 (Days 0) to Visit ***7 (April 2012)***[β] | All subjects |

*Refer to Section 5.2.3 for sub-cohort description.
NA=Not applicable
[β] ***i.e. end of RV season in China.*** **Amended: 05 August 2011**

### 5.7.3. Laboratory assays

**GE Stool analysis**

All stool samples collected during the study will be shipped frozen to a GSK Biologicals designated laboratory in China where aliquots will be prepared to be sent to a qualified lab and to GSK Biologicals, Belgium (or sponsor designated laboratory), for back-up. The tests in the laboratory at GSK Biologicals, Belgium will be performed only if necessary.

All GE stool samples will be analysed by Enzyme Linked Immunosorbent Assay (ELISA) for detection of RV antigen. If a stool sample tests positive for RV antigen, the sample will be tested by Polymerase Chain Reaction (PCR) to determine the G and P genotype. If any RV G1 strain is detected in the stool specimens from Visit 1 up to study end, viral strain of the vaccine will be differentiated from the wild type strain by sequence analysis or an equivalent approach.

**Serum analysis**

All serum samples collected during the study will be shipped frozen to a GSK Biologicals designated laboratory in China where aliquots will be prepared to be sent to a qualified lab and to GSK Biologicals, Belgium (or sponsor designated laboratory), for back-up, if necessary.

Serum anti-rotavirus IgA antibody concentrations will be measured in all serum samples collected at Visit 1, Visit 3 and Visit 6 using ELISA. The assay cut-off is 20 U/mL. Antibodies to all antigens contained in the co-administered vaccines will be measured at Visit 1 and Visit 5 (applicable only for subjects in the immunogenicity sub-cohort 2).

The laboratory assays to be performed are presented in Table 8.

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**Table 8 Laboratory Assays Amended: 05 August 2011**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | GSK Biologicals* |
| Serum | anti-diphtheria | ELISA** | ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-tetanus | ELISA** | ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-PT | ELISA** | ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-FHA | ELISA** | ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-PRN | ELISA** | ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | ***NIFDC*** | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | ***NIFDC*** | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | ***NIFDC*** | $ED_{50}$† | 1:8 | GSK Biologicals* |

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals in China.
**or Multiplex
ELISA = Enzyme Linked Immunosorbent Assay
***NIFDC*** = National Institute for ***Food and Drug Control*** **Amended: 05 August 2011**
U = Units; IU = International Units; EL.U = Elisa Units
†$ED_{50}$ = Estimated dose 50% is the seroprotective level.

Collected samples will be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

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## 5.7.4. Biological samples evaluation

### 5.7.4.1. Immunological read-outs

**Table 9 Immunological read-outs (Amended: 05 August 2011)**

| Blood sampling time-point | | Sub-cohort Name | No.of subjects | Component | Components priority rank |
|---|---|---|---|---|---|
| Type of contact and time-point | Sampling time-point | | | | |
| Visit 1 (days 0) | Pre-Vacc | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 1 0) | Pre-Vacc | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 3 2) | Post-Vacc § | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 3 (2) | Post-Vacc § | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| Visit 5 months 4) | Post-Vacc * | Immunogenicity Sub-cohort 2 | 300 | Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 6 1) | Efficacy follow up | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 6 (years 1) | Efficacy follow up | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| **GE stool analysis** | | | | | |
| Visit 1 (Days 0) to Visit ***7 (April 2012)***$^{\beta}$ | Throughout the study period | All subjects | | RV antigen | None |

D = Diphtheria, T = Tetanus
§ Post-Vacc 2: One month post Dose 2 of liquid HRV vaccine/placebo
*Post-Vacc 3: Two month post Dose 3 of OPV and one month post of Dose 3 of DTPa
$^{\beta}$ ***i.e. end of RV season in China.*** **Amended: 05 August 2011**

**Additional analysis**

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

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 9.

### 5.7.5. Immunological correlates of protection

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

Antibodies against the pertussis components PT, FHA and PRN will be measured by an ELISA technique developed by National Institute for the Control of Pharmaceutical and Biological Products (NICPBP). Purified pertussis antigens and references of anti-pertussis antibodies will be provided by GSK Biologicals. The cut-off of the test will be set at 5 ELISA units per ml (EL.U/ml). As per Chinese regulatory requirements, the clinical cut-off (vaccine response) for anti-PT and anti-FHA is defined at ≥20 EL.U/ml. The response to PRN is evaluated via the calculation of at least a 4-fold increase in antibody concentrations from pre to post- vaccination. No serological correlate of protection against pertussis has been established [Granström, 1987; Karpinsky, 1987]. Therefore seropositivity and vaccine response rates are used to evaluate vaccine immunogenicity. Subjects with antibody concentration below the cut-off of 5 EL.U/ml are considered seronegative.

## 6. STUDY VACCINES AND ADMINISTRATION

### 6.1. Description of study vaccines

The liquid HRV vaccine and placebo to be used in this study have been developed and manufactured by GSK Biologicals.

The DTPa vaccine to be used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 has been developed and manufactured by GSK Biologicals.

The OPV vaccine to be used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 has been developed and manufactured by Institute of Medical Biology Chinese Academy of Medical Sciences.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

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

Table 10 presents the formulation and presentation of study vaccines.

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**Table 10 Study vaccines**

| Vaccine Name | Treatment identifier | Formulation | Presentation | Volume |
|---|---|---|---|---|
| liquid HRV vaccine | Treatment 1 | RIX4414 HRV strain at least $10^{6.0}$ median $CCID_{50}$ Di-sodium Adipate 132.74 mg<br>DMEM 2.26 mg<br>Sucrose 48.8% (w/w)<br>water for injection q.s. as 1.5 mL | Liquid in a pre-filled oral applicator | 1.5 mL |
| Placebo | Treatment 2 | Di-sodium Adipate 132.74 mg<br>DMEM 2.26 mg<br>Sucrose 48.8% (w/w)<br>water for injection q.s. as 1.5 mL | Liquid in a pre-filled oral applicator | 1.5 mL |
| DTPa | Treatment3 | Diphtheria toxoid ≥ 30 international units (IU) 25 Limits of flocculation (Lf)<br>Tetanus toxoid ≥ 40 IU (10Lf)<br>Pertussis toxoid 25 µg Filamentous haemagglutinin 25 µg Pertactin 8 µg<br>Aluminium as salts 0.5 mg 2-phenoxyethanol ≤ 2.5 mg | Turbid white suspension in a pre-filled syringe | 0.5 mL |
| OPV | Treatment4 | per 0.1ml(2 drops) Total polio-virus, not less than 6.15lgCCID50<br>type1, not less than 6.0 lgCCID50<br>type2, not less than 5.0 lgCCID50<br>type3, not less than 5.5 lgCCID50 | liquid, oral | 1 mL/vial (2drops/dose) (10dose/vial) |

$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
DMEM = Dulbecco's Modified Eagle Medium

## 6.2. Storage and handling of study vaccines

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

The study vaccines must be stored at the defined temperature range (i.e. +2 to +8°C). Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines. The storage temperature of the vaccines will be monitored daily with temperature monitoring device(s) (at the minimum calibrated) and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation, i.e. temperature outside the range (0-8°C of storage), must be reported to the sponsor as soon as detected. Following an exposure to such a temperature deviation, vaccines will not be used until approval has been given by the Sponsor.

In case of temperature deviation between 0 and +2°C, the impacted study vaccines can still be administered, but the site must take adequate actions to go back to defined range +2 to +8°C and avoid re-occurrence of such a temperature deviation.

Please refer to the Module on Clinical Trial Supplies in the SPM for more details on the Temperature deviation process and the Module on Clinical Trial Supplies for details and instructions on the packaging and accountability of the study vaccines.

## 6.3. Dosage and administration of study vaccines

The pre-filled oral applicator is shaken well before use. The product (vaccine or placebo) should then be administered smoothly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration should occur in a quiet environment. Sufficient time should be allowed for the baby to swallow the liquid vaccine solution, to avoid regurgitation or vomiting. Should however the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered. The subject may continue to participate in the study. The oral vaccine intake characteristics (smooth vaccine intake, vaccine intake interrupted due to coughing or choking, regurgitation after vaccine intake, vomiting after vaccine intake) should be recorded in the eCRF.

The vaccination regimen is summarised in Table 11.

**Table 11 Dosage and administration**

| Type of contact and time-point | Doses | Treatment Group | Vaccine | Route [1] | Site [2] | Side [3] |
|---|---|---|---|---|---|---|
| Visit 1 (days 0); Visit 2 months 1) | 1 | Group HRV vaccine | liquid HRV vaccine | O | | |
| Visit 1 days 0); Visit 2 months 1 | 1 | Group Placebo | Placebo | O | | |
| Visit 2 months 1; Visit 3 months 2); Visit 4 months 3) | 1 | Group HRV vaccine<br>Group Placebo | DTPa | IM | Ant T | L |
| Visit 1 days 0); Visit 2 months 1; Visit 3 months 2) | 1 | Group HRV vaccine<br>Group Placebo | OPV | O | | |

[1]Oral (O)/ Intramuscular (IM)
[2]Thigh (T): Anterolateral (Ant)
[3]Left (L)

## 6.4. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see the Module on Clinical Trial Supplies in the SPM for details).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 6% additional doses will be supplied to replace those that are unusable.

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The investigator will use the SBIR to obtain the replacement vial number. The replacement numbers will be allocated by component. The system will ensure, in a blinded manner, that the replacement vial is of the same formulation as the randomised vaccine.

## 6.5. Contraindications to subsequent vaccination

***GSK Biologicals' liquid HRV vaccine or placebo:***

The following events constitute absolute contraindications to further administration of the liquid HRV vaccine or placebo. If any of these events occur during the study, the subject must not receive additional doses of the vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4.4).

- Hypersensitivity reaction following the administration of the liquid HRV vaccine or placebo.

- IS and any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following events constitute contraindications to administration of liquid HRV vaccine and placebo at that point in time; if any of these events occur 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.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. (Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.) All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness.

- GE within 7 days preceding the study vaccine administration.

***GSK Biologicals' DTPa vaccine:***

- DTPa vaccine should not be administered to subjects with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of DTPa vaccine.

- DTPa vaccine is contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances the vaccination course should be continued with diphtheria and tetanus vaccine.

## 6.6. Warnings and precautions

Warnings and precautions related to the liquid HRV vaccine

The liquid HRV vaccine should under no circumstances be injected

Warnings and precautions related to the DTPa.

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of DTPa vaccine should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication.

If any of the following events occur in temporal relation to receipt of DTPa, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

The following events were previously considered contra-indications for Diphtheria Tetanus whole cell Pertussis (DTPw) and can now be considered general precautions:

- Temperature of ≥ 40.5°C within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

A history of febrile convulsions and a family history of convulsive fits do not constitute contra-indications.

HIV infection is not considered as a contra-indication.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.

As for all diphtheria, tetanus and pertussis vaccines, the vaccine should be given deep intramuscularly and preferably at alternate injection sites.

DTPa vaccine should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

DTPa vaccine should under no circumstances be administered intravenously.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

For warnings and precautions related to the OPV vaccines, please refer to the respective product labels/package inserts.

## 6.7. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject's parents/LARs about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, are to be recorded in the eCRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

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 and any other symptom, to prevent fever from occurring (Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.).

Similarly, concomitant medication administered for the treatment of a SAE, at any time, must be recorded on the SAE screens in the eCRF. Refer to Section 8.1.2 for the definition of a SAE.

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### 6.7.1. Medications/products that may lead to the elimination of a subject from ATP analyses

The following criteria should be checked at each visit subsequent to the first vaccination 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 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 vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone 0.5 mg/kg/day, or equivalent. Inhaled and 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 the liquid HRV vaccine/placebo and ending 14 days after, with the exception of routine childhood vaccinations.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

### 6.7.2. Time window for recording concomitant medication/vaccination in the eCRF

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with the administration of each dose of study vaccine and ending 31 days after each dose of study vaccine must be recorded in the eCRF.

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding each dose of study vaccine must be recorded in the eCRF.

Any investigational medication or vaccine administered throughout the study (i.e. from Day 0 through Day 30 must be recorded in the eCRF.

***All medications given for the protocol defined GE episode that occur during the period starting with the administration of each dose of study vaccine and ending 31 days after each dose of study vaccine must be recorded both in the concomitant medication section of the eCRF and in the respective GE section of the eCRF. The medications given for the protocol defined GE episode occurring outside the window of 31 days post vaccination must be recorded only in the respective GE section of the eCRF.***
**Amended: 05 August 2011.**

### 6.8. Intercurrent medical conditions that may lead to elimination from an ATP cohort

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition likely to alter the immune response or are confirmed to have an immunodeficiency condition.

## 7. HEALTH ECONOMICS

Not applicable.

## 8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject's parents/LARs will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

### 8.1. Safety definitions

#### 8.1.1. Definition of an adverse event

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

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

**Examples of an AE include:**

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- 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 liquid HRV vaccine administration even though they 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 procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).

- 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.

- For therapeutic studies, 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).

NB AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

### 8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death.

b. Is life-threatening.

   NB: 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, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation.

   NB: In general, hospitalisation signifies that the subject has been admitted 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 also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, or

NB: 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 like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

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.

### 8.1.3. Solicited adverse events

The following general AEs presented in Table 12 will be solicited after administration of each liquid HRV vaccine/placebo in all subjects excluding subjects in immunogenicity sub-cohort 2:

**Table 12 Solicited general adverse events for liquid HRV vaccine/placebo (excluding subjects in immunogenicity sub-cohort 2)**

| |
|---|
| Cough/runny nose |
| Fever* |
| Irritability/Fussiness |
| Loss of appetite |
| Vomiting |
| Diarrhoea |

*(Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities)

The following general AEs presented in Table 13 will be solicited only for subjects in the immunogenicity sub-cohort 2:

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**Table 13 Solicited general adverse events for co-administered childhood vaccines**

| |
|---|
| Fever* |
| Irritability/Fussiness |
| Loss of appetite |
| Drowsiness |
| Gastrointestinal symptoms† |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain. These AEs are specific to OPV.

*(Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities).

NB Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

The following local AEs presented in Table 14 will be solicited only for subjects in the immunogenicity sub-cohort 2:

**Table 14 Solicited local adverse events for DTPa**

| |
|---|
| Pain at injection site |
| Redness at injection site |
| Swelling at injection site |

### 8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

## 8.2. Events or outcomes not qualifying as adverse events or serious adverse events

Not applicable.

## 8.3. Detecting and recording adverse events, serious adverse events

### 8.3.1. Time period for detecting and recording adverse events, serious adverse events

All AEs starting within 31days following administration of each dose of study vaccine must be recorded into the AE screen in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will be done throughout the study period for each subject. See Section 8.4 for instructions on reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 15.

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**Table 15 Reporting periods for adverse events, serious adverse events (Amended: 05 August 2011)**

| Study activity | Pre-Vacc* | V1 Dose 1 | 7 days post-vacc | 30 days post-vacc | V2 Dose 2 | 7 days post-vacc | 30 days post-vacc | V3 | V4 | V5 | V6 | *Study Conclusion V7* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D0 | | | M1 | | | M2 | M3 | M4 | Approximately One year of age | *April 2012*[β] |
| Reporting of solicited local and/or general AEs† | | | | | | | | | | | | |
| Reporting of unsolicited AEs | | | | | | | | | | | | |
| Reporting of SAEs** | | | | | | | | | | | | |
| Reporting of fatal SAEs or SAEs related to study participation or GSK concomitant products | | | | | | | | | | | | |

* i.e. consent obtained; Pre-vacc.: pre-vaccination; Vacc.: vaccination; Post-vacc.: post-vaccination; D: Day; M: Month V: Vaccination.

** during the entire study period ending one month (minimum 31 days) following the last vaccination

† Reporting of solicited general AEs for liquid HRV vaccine will be done by all subjects excluding subjects in immunogenicity sub-cohort 2. Reporting of solicited general AEs for OPV vaccine and solicited general and local AEs for DTPa vaccine will be done only by subjects in immunogenicity subs-cohort 2.

[β] ***i.e. end of RV season in China.*** **Amended: 05 August 2011**

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

### 8.3.2. Evaluation of adverse events and serious adverse events

#### 8.3.2.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting AEs, the subject's parents/LARs should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF or SAE Report screens as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to 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.

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### 8.3.2.2. Assessment of adverse events

#### *8.3.2.2.1. Assessment of intensity*

Intensity of the following AEs will be assessed as described in Table 16:

**Table 16 Intensity scales for solicited symptoms reported during the solicited follow-up period**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Fever* | | Record temperature in °C |
| Irritability/Fussiness | 0 | Behaviour as usual |
| | 1 | Mild: Crying more than usual/no effect on normal activity |
| | 2 | Moderate: Crying more than usual/interferes with normal activity |
| | 3 | Severe: Crying that cannot be comforted/prevents normal activity |
| Diarrhoea¶ | | Record the number of looser than normal stools /day |
| Vomiting§ | | Record the number of vomiting episodes/day |
| Loss of appetite | 0 | Appetite as usual |
| | 1 | Mild: Eating less than usual/no effect on normal activity |
| | 2 | Moderate: Eating less than usual/interferes with normal activity |
| | 3 | Severe: Not eating at all |
| Cough/runny nose | 0 | Normal |
| | 1 | Mild: Cough/runny nose which is easily tolerated |
| | 2 | Moderate: Cough/runny nose which interferes with daily activity |
| | 3 | Severe: Cough/runny nose which prevents daily activity |
| Drowsiness | 0 | Behaviour as usual |
| | 1 | Mild: Drowsiness easily tolerated |
| | 2 | Moderate: Drowsiness that interferes with normal activity |
| | 3 | Severe: Drowsiness that prevents normal activity |
| Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain) | 0 | Gastrointestinal symptoms normal |
| | 1 | Mild: Gastrointestinal symptoms that are easily tolerated |
| | 2 | Moderate: Gastrointestinal symptoms that interfere with normal activity |
| | 3 | Severe: Gastrointestinal symptoms that prevent normal activity |

*Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities
¶Diarrhoea is defined as passage of three or more looser than normal stools within a day.
§Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day

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**Table 17 Intensity scales used for diarrhoea, vomiting and fever reported during the solicited follow-up period**

| Adverse Experience | Intensity grade | Parameter |
|---|---|---|
| Diarrhoea | 0 | Normal (0 - 2 looser than normal stools/day) |
| | 1 | 3 looser than normal stools/day |
| | 2 | 4 - 5 looser than normal stools/day |
| | 3 | ≥ 6 looser than normal stools/day |
| Vomiting | 0 | Normal (no emesis) |
| | 1 | 1 episode of vomiting/day |
| | 2 | 2 episodes of vomiting/day |
| | 3 | ≥ 3 episodes of vomiting/day |
| Fever* | 0 | Axillary temperature < 37.1 °C |
| | 1 | Axillary temperature 37.1 °C - 37.5 °C |
| | 2 | Axillary temperature 37.6 °C - 39.0 °C |
| | 3 | Axillary temperature > 39.0 °C |
| Fever** | 0 | Axillary temperature < 37.5°C |
| | 1 | Axillary temperature ≥ 37.5 – ≤ 38.0°C |
| | 2 | Axillary temperature > 38.0 – ≤ 39.0°C |
| | 3 | Axillary temperature > 39.0°C |

*The maximum intensity of fever using the grading scale as defined by Chinese authorities.
**The maximum intensity of fever using the grading scale as defined by GSK Biologicals.

Intensity of the following solicited local AEs will be assessed as described in Table 18.

**Table 18 Intensity scales for solicited local symptoms**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Pain at injection site | 0 | None |
| | 1 | Mild: Minor reaction to touch |
| | 2 | Moderate: Cries/protests on touch |
| | 3 | Severe: Cries when limb is moved/spontaneously painful |
| Redness at injection site | | Record greatest surface diameter in mm |
| Swelling at injection site | | Record greatest surface diameter in mm |

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals using the guidelines of grading standards for AEs set by the Chinese authorities as follows:

| | | |
|---|---|---|
| 0 | : | Absent |
| 1 | : | < 15 mm |
| 2 | : | ≥ 15 mm and ≤ 30 mm |
| 3 | : | > 30 mm |

The investigator will assess the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

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

| | | |
|---|---|---|
| 1 (mild) | = | An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. |
| 2 (moderate) | = | An AE which is sufficiently discomforting to interfere with normal everyday activities. |
| 3 (severe) | = | An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at a day-care centre and would cause the parents/LARs to seek medical advice) |

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

#### *8.3.2.2.2. 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 plausible causes, based on 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 in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

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

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*Is there a reasonable possibility that the AE may have been caused by the liquid HRV vaccine?*

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

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined 'serious' (see Section 8.1.2 for definition of SAE), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

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

#### 8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study will be assessed as:

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

#### 8.3.2.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parents/LARs will be asked if the subject received medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in eCRF.

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## 8.4. Reporting and follow-up of adverse events, serious adverse events and pregnancies

### 8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs will be reported promptly to GSK as described in Table 19 once the investigator determines that the event meets the protocol definition of an SAE.

**Table 19 Time frames for submitting SAEs and other events reports to GSK Biologicals**

| Type of Event | Initial Reports | | Follow-up of Relevant Information on a Previous Report | |
|---|---|---|---|---|
| | Time Frame | Documents | Time Frame | Documents |
| All SAEs | 24 hours* | SAE screen | 24 hours* | SAE report/SAE screen |

* Time frame allowed after receipt or awareness of the information.

In case the electronic reporting system is temporarily unavailable, a backup system is in place. Please refer to Section 8.4.3 for a detailed description

**Study Contact for Reporting SAEs**

Please see the Sponsor Information Sheet for contact details.

**Back-up Study Contact for Reporting SAEs**

GSK Biologicals Clinical Safety and Pharamcovigilance

Fax: [redacted] or [redacted]

24/24 hour and 7/7 day availability

### 8.4.2. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1 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.

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 SAEs that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

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### 8.4.3. Completion and transmission of SAEs reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional relevant information is received WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

#### 8.4.3.1. Back-up system in case the electronic SAE reporting system does not work

If the SAE reporting system has been down for 24 hours, the investigator or his/her delegate should fax an SAE report form directly to the GSK Central Safety department (please refer to Section 8.4.1) within 24 hours. The maximum timeline for reporting SAEs to central safety is therefore 48 hours.

NB. This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow.

As soon as the electronic reporting system is working again, the investigator or delegate must update the SAE screens in the eCRF within 24 hours.

The final valid information for regulatory reporting will be the information reported through the electronic system.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be sent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information.

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

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

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### 8.4.4. Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

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, or until the event is otherwise explained, or the subject is lost to follow-up.

- Or, in the case of other non-serious AEs, until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the Site Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of additional clinical examinations/tests 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.

## 8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.7.

## 8.6. Unblinding

GSK Biologicals' policy (incorporating ICH E2A 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 GSK Biologicals' Central Safety physician is responsible for

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unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (refer to Section 8.4.1).

## 8.7. Emergency unblinding

The investigator, or other physician managing the subject, should contact GSK Biologicals' Central Safety Physician to discuss the need for emergency unblinding. Alternatively the investigator may contact the local contact who will contact the GSK Central Safety Physician.

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

An investigator should request for unblinding of the subject's treatment code only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study vaccines/product(s) is essential for the clinical management or welfare of the subject.

The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s)/product(s).

| **GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)** |
|---|
| Phones for 7/7 day availability:<br><br>Outside US/Canada:<br>[redacted] (GSK Biologicals Central Safety Physician)<br><br>Back-up mobile phone contact (all countries):<br>[redacted] |

## 8.8. Subject card

Subjects' parents/LARs must be provided with the address and telephone number of the main contact for information about the trial.

Investigator/delegate should therefore provide a "subject card" to each subject's parents/LARs. The aim of this card is to inform any physician having to deal with a subject in an emergency situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information.

Subjects' parents/LARs must be instructed to keep these cards in their possession at all times.

## 8.9. Assessment of GE episodes

Any GE episode (defined as diarrhoea with or without vomiting) occurring starting from Visit 1 to study end should be documented using the GE diary card. The following information will be collected on the GE diary card during each GE episode: Axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given. The information collected on the GE diary card will allow the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

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

In the 20-point scoring system, points will be assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalisation (hospitalised subjects will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 20.

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**Table 20 The 20-point scoring system to determine the intensity of GE episodes reported during the study**

| Adverse Experience | Points |
|---|---|
| Duration of looser than normal stools (days) | |
| 1-4 | 1 |
| 5 | 2 |
| ≥ 6 | 3 |
| Maximum number of looser than normal stools /24 hours | |
| 1-3 | 1 |
| 4-5 | 2 |
| ≥ 6 | 3 |
| Duration of vomiting (days) | |
| 1 | 1 |
| 2 | 2 |
| ≥ 3 | 3 |
| Maximum number of episodes of vomiting/24 hours | |
| 1 | 1 |
| 2-4 | 2 |
| ≥ 5 | 3 |
| Fever∗<br>Axillary | |
| 36.6 – 37.9°C | 1 |
| 38.0 – 38.4°C | 2 |
| ≥ 38.5°C | 3 |
| Dehydration | |
| 1-5% | 2 |
| ≥ 6% | 3 |
| Treatment | |
| Rehydration | 1 |
| Hospitalisation | 2 |

∗The highest temperature recorded during the episode will be scored.

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

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

# 9. SUBJECT COMPLETION AND WITHDRAWAL

## 9.1. Subject completion

A subject who returns for the concluding visit in the protocol is considered to have completed the study.

## 9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/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 8.4).

Withdrawals will not be replaced.

### 9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered 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 in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject's parents/ LARs, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

### 9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to 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 vaccine 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 vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parents/ LARs or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-SAE.
- Other (specify).

# 10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

## 10.1. Primary endpoint

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

## 10.2. Secondary endpoints

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***). **Amended: 05 August 2011**

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*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as GMC at Visit 3 and at Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  - Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

## 10.3. Estimated sample size

Target enrolment will be 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated rate ***of non evaluable subjects*** is 20%.

Considering 1:1 randomisation ratio and various incidence rates, Table 21 provides the power to observe a lower limit of the 95% CI for vaccine efficacy to be above 0% and 10%.

For a 2% attack rate of RV GE in the placebo group from 2 weeks post Dose 2 to ***end of efficacy follow-up period***, and if the vaccine efficacy is 80%, the study has 95.8% power to observe a 95% CI for the vaccine efficacy that would be above 10%. It is expected to observe a total of 40 ***severe*** RV GE cases during the efficacy follow-up period in the total vaccinated cohort. **Amended: 05 August 2011**

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**Table 21 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 2600 evaluable subjects – 1300 subjects in HRV group and 1300 subject in the placebo group, power based on 1,000 simulations using Proc StatXact) Amended: 05 August 2011**

| Incidence rate in the Placebo for severe RV GE | VE (%) | Power to have a lower limit of the 95%CI on VE ≥ 0% | Power to have a lower limit of the 95%CI on VE ≥ 10% |
|---|---|---|---|
| ***1%*** | ***70*** | ***54.5%*** | ***44.2%*** |
| | ***80*** | ***69.6%*** | ***60.8%*** |
| 1.5% | 70 | 74.4% | 65.1% |
| | 80 | 87.8% | 82.7% |
| 2%* | 70 | 85.1% | 77.2% |
| | 80** | 97.6% | 95.8% |
| 2.5% | 70 | 92.7% | 87.8% |
| | 80 | 99.4% | 98.6% |
| 3% | 70 | 96.4% | 92.3% |
| | 80 | 99.4% | 99.3% |

*anticipated rate in the Placebo for severe RV GE.
VE - Vaccine Efficacy. CI-Confidence Interval
**anticipated vaccine efficacy
Attack Rate (AR) = 1.5% [1.0%; 2.3%], VE = 95.3% [73.1%;99.9%].

## 10.4. Study cohorts to be evaluated

### 10.4.1. Total vaccinated cohort

The total vaccinated cohort will include all subjects with at least one dose of the liquid HRV vaccine or placebo administration documented:

- A safety analysis based on the total vaccinated cohort will include all vaccinated subjects,
- An immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects from the immunogenicity sub-cohorts for whom immunogenicity data are available,
- An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available.

### 10.4.2. According-To-Protocol cohort for analysis of safety

The ATP cohort for safety will include all vaccinated subjects:

- who have received at least one dose of HRV vaccine/Placebo according to their random assignment.
- for whom the randomisation code has not been broken, who have not received a vaccine forbidden by or not specified in the protocol.

### 10.4.3. According-to-protocol cohort for analysis of efficacy

The ATP cohort for efficacy will include all subjects from ATP cohort for safety.

- 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 received 2 doses of the liquid HRV vaccine or placebo,
- who have entered the efficacy surveillance period:
  - have follow-up beyond 2 weeks post Dose 2 of study vaccination
  - who have no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks post Dose 2 of liquid HRV vaccine or placebo.

### 10.4.4. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include subjects in the immunogenicity sub-cohorts 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 the protocol defined age interval),
- who comply with vaccination schedule of liquid HRV vaccine or placebo,
- who comply with blood sampling schedule,
- for whom immunogenicity data was available, at pre and post sampling time-points,
- who have no concomitant infection unrelated to the vaccine which may influence the immune response,
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 3,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1.

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

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

## 10.5. Derived and transformed data

**Demography**

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

**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.

***The subjects, who have completed Visit 6 and have not given their consent to participate in the extension follow-up, will be considered as dropouts from the study. The ATP cohort for the analysis of efficacy will include all the subjects who have satisfied the points mentioned in the section 10.4.3.*** **Amended: 05 August 2011**

**Immunogenicity**

The cut-off value is defined by the laboratory before the analysis and is described in section 5.7.3.

- 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. The following seropositivity thresholds are applicable:
  - Anti-PT and anti-FHA antibody concentrations Greater than or equal to ≥ 20 El.U/ml
  - Anti-PRN should be at least a 4-fold increase in antibody concentration for the ratio of post-vaccination to pre-vaccination
  - Anti rotavirus antibody IgA antibody concentration ≥ to 20 U/mL

- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
  - Anti-diphtheria antibody concentrations ≥ 0.1 IU/ml.
  - Anti-tetanus antibody concentrations ≥ 0.1 IU/ml.
  - Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8.
- Seroconversion is defined as the appearance of IgA antibodies (i.e. concentration greater than or equal to the cut-off value) in the serum of subjects who were seronegative before vaccination.
- The GMCs calculations are performed by taking the anti-log of the mean of the log concentrations 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 the immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

**Safety/Reactogenicity**

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

## 10.6. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

### 10.6.1. Sequence of analyses

Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ***study conclusion***, an annex report will present ***all*** data up to ***study conclusion***. ***Immunogenicity analysis will be done with the case triggered analysis only if the serological results are available at that point in time or it will be presented in the annex report.***
**Amended: 05 August 2011**

### 10.6.2. Statistical considerations for interim analyses

No interim analysis is planned for the study.

## 10.7. Statistical methods

### 10.7.1. 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 and overall. The racial and gender composition will be presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo will be calculated per group and over all. The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group. The percentages of subjects who received concomitant and intercurrent vaccinations will be tabulated by group.

### 10.7.2. Analysis of efficacy

The ATP cohort for efficacy will be used for the primary analysis of efficacy. An analysis of efficacy based on the total vaccinated cohort will also be performed.

Vaccine efficacy will be calculated, with their 95% CI against:

- severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to each non-G1 type during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe all cause GE during the efficacy follow-up period.
- Vaccine efficacy will also be derived from a Cox regression model on the time to first event with censoring for subjects without an event as an additional supportive & exploratory analysis.
- ***Vaccine efficacy analysis will also be performed on the data collected from 2 weeks post dose 2 of HRV vaccine /placebo up to visit 6. This will be presented as an additional supportive analysis.*** **Amended: 05 August 2011**

The same analysis will also be performed on Total Vaccinated Cohort from dose 1 to study end.

### 10.7.3. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for the analysis of immunogenicity. If the percent of enrolled subjects excluded from this ATP cohort is more than 5%, a second analysis based on the Total Vaccinated cohort will be performed to complement the ATP analysis.

**For subjects in the immunogenicity sub-cohort 1:**

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

- Seroconversion rates at Visit 3 and seropositivity rate at Visit 6 and their exact 95% CI will be calculated.
- GMCs at Visit 3 and Visit 6 and their 95% CI will be calculated.
- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 will be displayed using reverse cumulative curves (RCCs).
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the placebo group will be computed.

**For subjects in the immunogenicity sub-cohort 2:**

For each treatment group, at each time-point that anti-rotavirus IgA anti-PT, anti-FHA, anti-PRN and anti-poliovirus serotype 1, 2 and 3 is measured

- Seroconversion rates at Visit 3 and seropositivity rate at Visit 6 and their exact 95% CI will be calculated.
- GMCs at Visit 3 and Visit 6 and their 95% CI will be calculated.
- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 will be displayed using reverse cumulative curves (RCCs).
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the placebo group will be computed.
- Seroprotection rates and their exact 95% CIs for antibodies against diphtheria and tetanus and poliovirus types 1, 2 and 3 one month post Dose 3 of DTPa will be calculated.
- Seropositivity rates and their exact 95% CIs for antibodies against PT, FHA, PRN and poliovirus types 1, 2 and 3 one month post Dose 3 of DTPa will be tabulated.

- GMT/GMCs and their 95% CIs for antibodies against the vaccine antigens PT, FHA, PRN and poliovirus types 1, 2 and 3 one month post Dose 3 of DTPa will be calculated.

### 10.7.4. Analysis of safety

Note: Intensity of fever will be assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale will be performed separately.

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.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each dose, for overall doses and per subject. The same calculations will be performed for any grade 3 (solicited or unsolicited) symptoms and for any (solicited or unsolicited) symptom related to vaccination.

The incidence, with exact 95% CI, of each individual solicited general symptom, will be calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects with at least one local AE (solicited and unsolicited) after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination will be tabulated with exact 95% CI. The same calculations will be performed for any grade 3 (solicited or unsolicited)

symptoms, grade 3 related symptoms and for any symptoms requiring medical attention.

- The percentage of subjects reporting each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa during the 8-day (Days 0–7) follow-up period with exact 95% CI will be tabulated.
- Occurrence of fever and related fever will be reported per 0.5°C cumulative temperature increments.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

**For all subjects:**

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

SAEs reported during the study period (i.e. from first vaccine dose till study end) will be described in detail.

***There will be a retrospective follow-up on SAEs for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2 and this will documented in the eCRF.*** **Amended: 05 August 2011**

# 11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

## 11.1. Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

## 11.2. Monitoring by GSK Biologicals

Monitoring visits by a GSK Site Monitor 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).

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF entries will serve as the source document.

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any amendments, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

## 11.3. Archiving of data at study sites

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); 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, 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.

## 11.4. Audits

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

## 11.5. Posting of information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

## 11.6. Ownership, confidentiality and publication

### 11.6.1. 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.

### 11.6.2. 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

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investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) 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.

### 11.6.3. 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 twenty-one working days, or at least 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.

### 11.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development.

In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

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# Appendix A AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

| **GlaxoSmithKline Biologicals**<br>Clinical Research & Development<br>**Protocol Amendment 1** | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Amendment number:** | Amendment 1 |
| **Amendment date:** | 02 September 2010 |
| **Co-ordinating author:** | [redacted] Scientific Writer |
| **Rationale/background for changes:** The following changes have been made in the protocol | |
| **Amended text has been indicated in *bold italics* in the following sections:**<br>**Section 5.2.2.1: Randomisation of supplies**<br>The randomisation will be performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.<br><br>To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, ***6%*** ~~an~~ over-randomisation of supplies will be prepared.<br><br>The vaccine doses will be distributed to the study centres while respecting the randomisation block size. | |
| **Section 5.2.3: Randomisation of subjects to assay sub-cohorts**<br><br>***Randomisation for all the sub-cohorts will be done in parallel.*** ~~Randomisation order for the immunogenicity sub-cohorts will be as follows, the 1st 600 subjects will be randomised into immunogenicity sub-cohort 1 and the final 300 subjects will be randomised into immunogenicity sub-cohort 2.~~ Blood samples will be collected from both the sub-cohorts of subjects:<br><br>• Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).<br><br>• Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300). | |

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**Section 6.7.1: Medications/products that may lead to the elimination of a subject from ATP analyses**

- Administration of a vaccine not foreseen by the study protocol during the period starting from ***14*** ~~30~~ days before each dose of the liquid HRV vaccine/placebo and ending ***14*** ~~30~~ days after, with the exception of routine childhood vaccinations.

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113808 (ROTA-075)
Amendment 2

# GlaxoSmithKline Biologicals

Clinical Research & Development

## Protocol Amendment 2

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Amendment number:** | Amendment 2 |
| **Amendment date:** | 05 August 2011 |
| **Co-ordinating author:** | [redacted] Scientific Writers |

**Rationale/background for changes:**
Based on the preliminary review of GE episodes reported to date prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seems lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up needs to be extended till April 2012 (i.e. end of RV season in China).

In addition:

- The names of the co-ordinating and contributing authors have been updated on the title page.
- A few minor corrections such as typos and inconsistencies have been corrected.

**Amended text has been indicated in *bold italics* in the following sections:**

| | |
|---|---|
| **Contributing authors** | [redacted] ***Clinical Immunology representative*** |

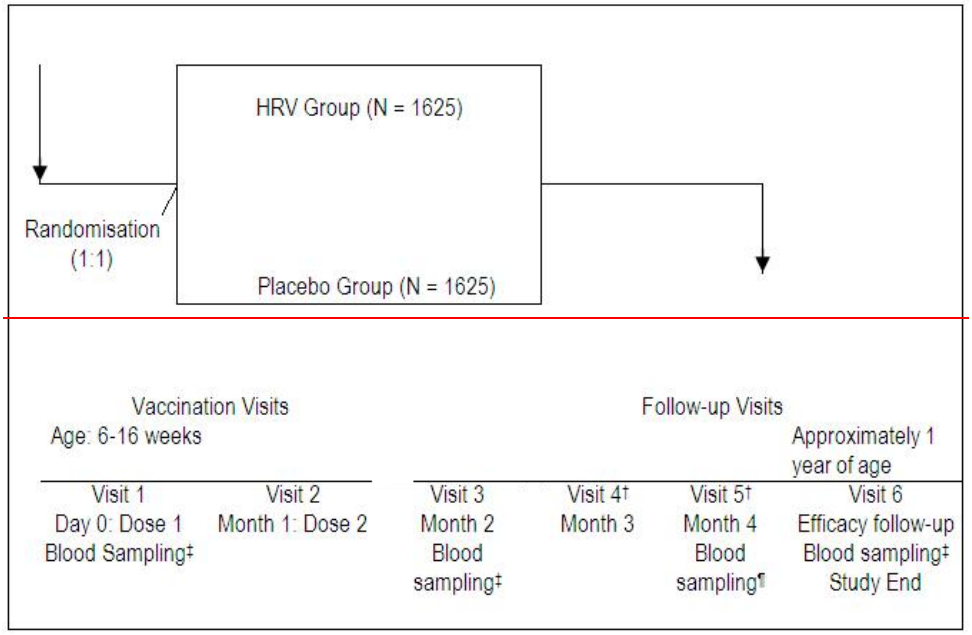
**List of Abbreviations**

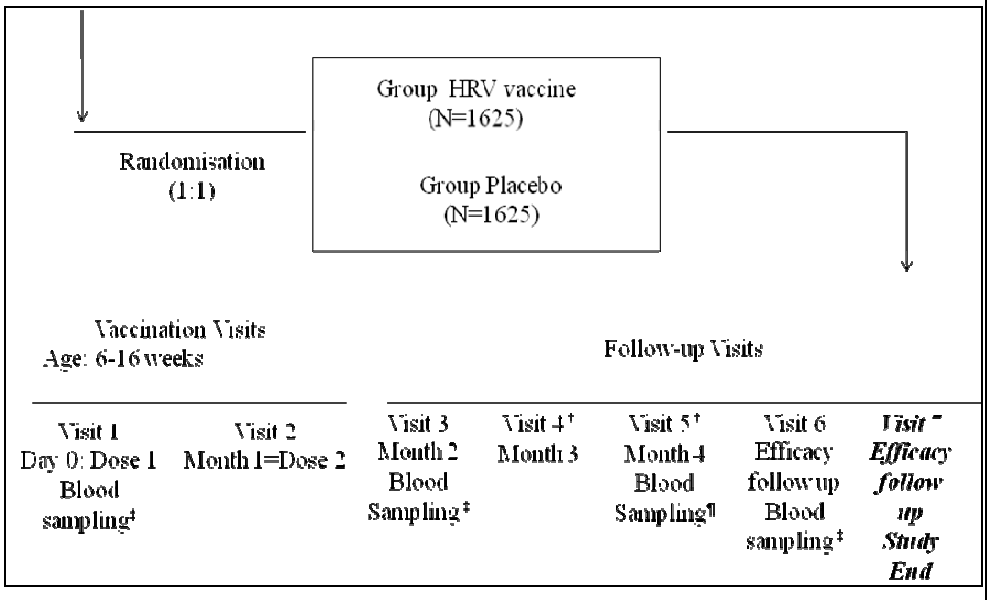
| | |
|---|---|
| ***NIFDC*** | ***National Institute for Food and Drug Control*** |

**1.1: Background**
The liquid HRV vaccine is currently registered in ~~over 50 countries~~ ***at least 77 countries*** worldwide including Mexico, Brazil, Australia and the European Union.

**In the Synopsis and Section 1.2: Rationale for the study and study design**
The primary objective of this study is to evaluate the efficacy of the liquid HRV vaccine to prevent severe RV GE during the efficacy follow-up period. There will be an efficacy follow-up starting 2 weeks after the second dose of study vaccination till ~~the infants are one year of age~~ ***April 2012 (i.e. end of RV season in China)***.

**In the Synopsis and Section 3: Study Design Overview**




N: Number of subjects planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort2.
‡Blood will be drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood will be drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 will receive a dose of OPV at Visit 1, Visit 2 and Visit 3; and will receive a dose of DTPa at Visit 2, Visit 3 and Visit 4

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- Duration of the study: ***The subjects will be followed until April 2012 (i.e. end of RV season in China).*** The intended duration of the study, per subject, will ~~be till the subject is one year of age~~ ***not exceed a maximum of 21 months***. The study will have a single epoch as follows.
  - Primary: Primary starting Visit 1 (Day 0) and ending Visit ~~6~~***7*** ~~(1 year of age)~~ ***(April 2012 i.e. end of RV season in China)***.
- Recording of SAEs throughout the study period for all subjects.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.***
- For each GE episode occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after GE symptoms begin.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.***
- ***All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).***
- ***The additional informed consent will be taken for the extended follow-up.***
- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ~~when all subjects have reached one year of age~~ ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ~~all subjects reach one year of age~~ ***study conclusion***, an annex report will present ***all*** ~~the efficacy/safety~~ data up to ~~one year of age~~ ***study conclusion***.

**Section 4.1: Number of subjects/centres**

- The intended duration of the study, per subject, will ~~be till the subject is one year of age~~ ***not exceed a maximum of 21 months***.

**Section 5.5: Outline of study procedures**
**Table 5: List of study procedures**

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| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | *Visit 7* |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | *Approximately* Years 1 of age | *April 2012*[B] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | *Efficacy follow up* |
| Informed consent | ● | | | | | | |
| ***Re-consenting for Visit 7 follow-up*** | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | O | O | O | O | O | O |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approximately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approximately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approximately 3mL: sub-cohort 2) | ● (Approxima-tely 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+DTPa) | ● (OPV+DTPa) | ● (DTPa) | | | |

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| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | *Visit 7* |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | *Approximately* Years 1 of age | *April 2012*[8] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | *Efficacy follow up* |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of ~~non-SAEs~~ ***unsolicited AEs*** within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | O | O | O | O | O | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | ● | ● |
| Study Conclusion | | | | | | ● | ● |

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● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
*Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort 2.
**Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
***β i.e. end of RV season in China.***

**Table 6: Intervals between study visits**

| Interval | Optimal length of interval [1] | Maximum interval allowed [2] |
|---|---|---|
| 1 (Visit 1) →(Visit 2) | 30-48 days | 21-48 days |
| 2 ((Visit 2 →(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3 →(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | ~~by one year of age~~ ***1 year of age ± 2 weeks[γ]*** | ***1 year of age ± 30 days*** |
| ***6 (Visit 6) → (Visit 7)*** | ***01 April 2012 to 30 April 2012[γ]*** | ***01 April 2012 to 31 May 2012*** |

[1]. Whenever possible the investigator should arrange study visits within this interval
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they make the study visit outside this interval
Note: The date of the previous visit serves as the reference date for intervals between study visits. Refer to section 3 for details on the study visits applicable to the subjects in the study.
***[γ] It is a defined time point for follow up visit in a range and not an interval***

**Section 5.6.3.12: Recording GE occurring throughout the study period in a GE diary card**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.3.13: Collection of stool samples in case the child develops GE**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.3.14: Return of diary cards and GE diary cards**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.3.15: Diary card and GE diary card transcription by investigator**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.4: Procedures during Efficacy follow-up *(Visit 6)***

***For subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2:***

***The additional consent will be obtained from the subject's parents/LARs. Retrospective data on intercurrent medical condition, concomitant medication/vaccination, GE episodes and SAEs will also be collected.***

***For subjects who are returning for Visit 6 after the implementation of protocol amendment 2:***
Note that some of the procedures to be performed during the follow-up visits (such as physical examination, blood sampling, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of ***S***AEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11. ***For the participation in the extended follow-up till Visit 7, additional consent of subject's parents/LARs will be obtained.***

***Section 5.6.5: Procedures during Efficacy follow-up (Visit 7)***
***Note that some of the procedures to be performed during the follow-up visits (such as physical examination, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of SAEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11.***

**Section 5.7.2: Biological samples**
**Table 7: Biological samples**

| Sample type | Quantity | Unit | Time-point | Sub-cohort Name* |
|---|---|---|---|---|
| Blood | Approximately 3 | ml | Schedule (Visit 1) Days 0 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 4 .5 | ml | Schedule (Visit 1) Days 0 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) Months 2 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) Months 2 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 5) Months 4 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) Years 1 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) Years 1 | Immunogenicity Sub-cohort 2 |
| Stool | NA | NA | Schedule From Visit 1 (Days 0) to Visit ~~6 (1 year)~~ ***7 (April 2012)***$^{\beta}$ | All subjects |

Refer to Section 5.2.3 for sub-cohort description.
NA=Not applicable
$^{\beta}$ ***i.e end of RV season in China.***

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**Section 5.7.2: Biological samples**
**Table 9: Immunological read-outs**

| Blood sampling time-point | | Sub-cohort Name | No.of subjects | Component | Components priority rank |
|---|---|---|---|---|---|
| Type of contact and time-point | Sampling time-point | | | | |
| Visit 1 (Days 0) | Pre-Vacc | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 1 (Days 0) | Pre-Vacc | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 3 (Months 2) | Post-Vacc § | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 3 (Months 2) | Post-Vacc § | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| Visit 5 (Months 4) | Post-Vacc * | Immunogenicity Sub-cohort 2 | 300 | Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 6 (Years 1) | Efficacy follow up | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 6 (Years 1) | Efficacy follow up | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| **GE stool analysis** | | | | | |
| Visit 1 (Days 0) to Visit ~~6 (At 1 year of age)~~ ***7 (April 2012)$^{\beta}$*** | Throughout the study period | All subjects | | RV antigen | None |

D = Diphtheria, T = Tetanus
§ Post-Vacc 2: One month post Dose 2 of liquid HRV vaccine/placebo
*Post-Vacc 3: Two month post Dose 3 of OPV and one month post of Dose 3 of DTPa
***$^{\beta}$ i.e. end of RV season in China.***

**Section 5.7.3: Laboratory assays**
**Table 8: Laboratory assays**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | GSK Biologicals* |
| Serum | anti-diphtheria | ELISA** | ~~NICPBP~~ ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-tetanus | ELISA** | ~~NICPBP~~ ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-PT | ELISA** | ~~NICPBP~~ ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-FHA | ELISA** | ~~NICPBP~~ ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-PRN | ELISA** | ~~NICPBP~~ ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | ~~NICPBP~~ ***NIFDC*** | ED50† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | ~~NICPBP~~ ***NIFDC*** | ED50† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | ~~NICPBP~~ ***NIFDC*** | ED50† | 1:8 | GSK Biologicals* |

GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals in China.
**or Multiplex
ELISA = Enzyme Linked Immunosorbent Assay
~~NICPBP~~ ***NIFDC*** = National Institute for ~~the control of Pharmaceutical and Biological~~ ~~Product~~ ***Food and Drug Control***
U = Units; IU = International Units; EL.U = Elisa Units
†ED50 = Estimated dose 50% is the seroprotective level.

**Section 6.7.2: Time window for recording concomitant medication/vaccination in the eCRF**

***All medications given for the protocol defined GE episode that occur during the period starting with the administration of each dose of study vaccine and ending 31 days after each dose of study vaccine must be recorded both in the concomitant medication section of the eCRF and in the respective GE section of the eCRF. The medications given for the protocol defined GE episode occurring outside the window of 31 days post vaccination must be recorded only in the respective GE section of the eCRF.***

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**Section 8.3.1:Time period for detecting and recording adverse events, serious adverse events**
**Table 15: Reporting periods for adverse events, serious adverse events**

| Study activity | Pre Vacc* | V1 Dose 1 | 7 days post-vacc | 30 days post-vacc | V2 Dose 2 | 7 days post-vacc | 30 days post-vacc | V3 | V4 | V5 | V6 | *Study Conclusion V7* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D0 | | | M1 | | | M2 | M3 | M4 | *Approximately* One year of age | *April 2012[β]* |
| Reporting of solicited local and/or general AEs† | | | | | | | | | | | | |
| Reporting of unsolicited AEs | | | | | | | | | | | | |
| Reporting of SAEs** | | | | | | | | | | | | |
| Reporting of fatal SAEs or SAEs related to study participation or GSK concomitant products | | | | | | | | | | | | |

* i.e. consent obtained; Pre-vacc.: pre-vaccination; Vacc.: vaccination; Post-vacc.: post-vaccination; D: Day; M: Month V: Vaccination.

** during the entire study period ending one month (minimum 31 days) following the last vaccination

† Reporting of solicited general AEs for liquid HRV vaccine will be done by all subjects excluding subjects in immunogenicity sub-cohort 2. Reporting of solicited general AEs for OPV vaccine and solicited general and local AEs for DTPa vaccine will be done only by subjects in immunogenicity subs-cohort 2.

***[β] i.e. end of RV season in China.***

**In the Synopsis and Section 10.1: Primary endpoint**

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period ***(two weeks post-Dose 2 till Visit 7)***.

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**In the Synopsis and Section 10.2: Secondary endpoints**

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).

Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).

**Section 10.3: Estimated sample size**

Target enrolment will be 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated ~~dropout~~ rate ***of non evaluable subjects*** is 20%.

For a 2% attack rate of RV GE in the placebo group from 2 weeks post Dose 2 ~~up~~ to ~~one year of age~~ ***end of efficacy follow-up period***, and if the vaccine efficacy is 80%, the study has 95.8% power to observe a 95% CI for the vaccine efficacy that would be above 10%. It is expected to observe a total of 40 ***severe*** RV GE cases during the efficacy follow-up period in the total vaccinated cohort.

**Table 21 : Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 2600 evaluable subjects – 1300 subjects in HRV group and 1300 subject in the placebo group, power based on 1,000 simulations using Proc StatXact)**

| Incidence rate in the Placebo for severe RV GE | VE (%) | Power to have a lower limit of the 95%CI on VE ≥ 0% | Power to have a lower limit of the 95%CI on VE ≥ 10% |
|---|---|---|---|
| ***1%*** | ***70*** | ***54.5%*** | ***44.2%*** |
| | ***80*** | ***69.6%*** | ***60.8%*** |
| 1.5% | 70 | 74.4% | 65.1% |
| | 80 | 87.8% | 82.7% |
| 2%* | 70 | 85.1% | 77.2% |
| | 80** | 97.6% | 95.8% |
| 2.5% | 70 | 92.7% | 87.8% |
| | 80 | 99.4% | 98.6% |
| 3% | 70 | 96.4% | 92.3% |
| | 80 | 99.4% | 99.3% |

| |
|---|
| *anticipated rate in the Placebo for severe RV GE.<br>VE - Vaccine Efficacy. CI-Confidence Interval<br>**anticipated vaccine efficacy<br>Attack Rate (AR) = 1.5% [1.0%; 2.3%], VE = 95.3% [73.1%;99.9%]. |
| **Section 10.5: Derived and transformed data**<br>**Effiacy**<br>***The subjects, who have completed Visit 6 and have not given their consent to participate in the extension follow-up, will be considered as dropouts from the study. The ATP cohort for the analysis of efficacy will include all the subjects who have satisfied the points mentioned in the section 10.4.3.*** |
| **Section 10.6.1: Sequence of analyses**<br>Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ~~when all subjects have reached one year of age~~ ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ~~all subjects reach one year of age~~ ***study conclusion***, an annex report will present ~~the efficacy/safety~~ ***all*** data up to ~~one year of age~~ ***study conclusion***.<br>***Immunogenicity analysis will be done with the case triggered analysis only if the serological results are available at that point in time or it will be presented in the annex report.*** |
| **Section 10.7.2 Analysis of efficacy**<br>***Vaccine efficacy analysis will also be performed on the data collected from 2 weeks post dose 2 of HRV vaccine/placebo up to visit 6. This will be presented as an additional supportive analysis.*** |
| **Section 10.7.4 Analysis of safety**<br>***There will be a retrospective follow-up on SAEs for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2and this will document in the eCRF.*** |

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113808 (ROTA-075)
Final

## Protocol Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 . |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted] Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | [redacted] |
| **Date** | 7 July 2010 |

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113808 (ROTA-075)
Final

## Protocol Investigator Agreement

**I agree:**

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (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.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- 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 documents required by regulatory agencies for this study.

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113808 (ROTA-075)
Final

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | [redacted] |
| **Signature** | [redacted] |
| **Date** | 20/June/2010 |

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113808 (ROTA-075)
Amendment 1

# Protocol Amendment 1 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 |
| **Date of protocol amendment** | Amendment 1: 2 Sep 2010 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted]<br>Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | [redacted] |
| **Date** | 10 Sep 2010 |

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113808 (ROTA-075)
Amendment 1

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 |
| **Date of protocol amendment** | Amendment 1: 2 Sep 2010 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | [redacted] |
| **Signature** | |
| **Date** | 03 - Nov-2010 |

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113808 (ROTA-075)
Amendment 2

# Protocol Amendment 2 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010. |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted]<br>Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | [redacted] |
| **Date** | Aug 22, 2011 |

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| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | [redacted] |
| **Signature** | |
| **Date** | 23-08-2011 |

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# Sample Case Report Form

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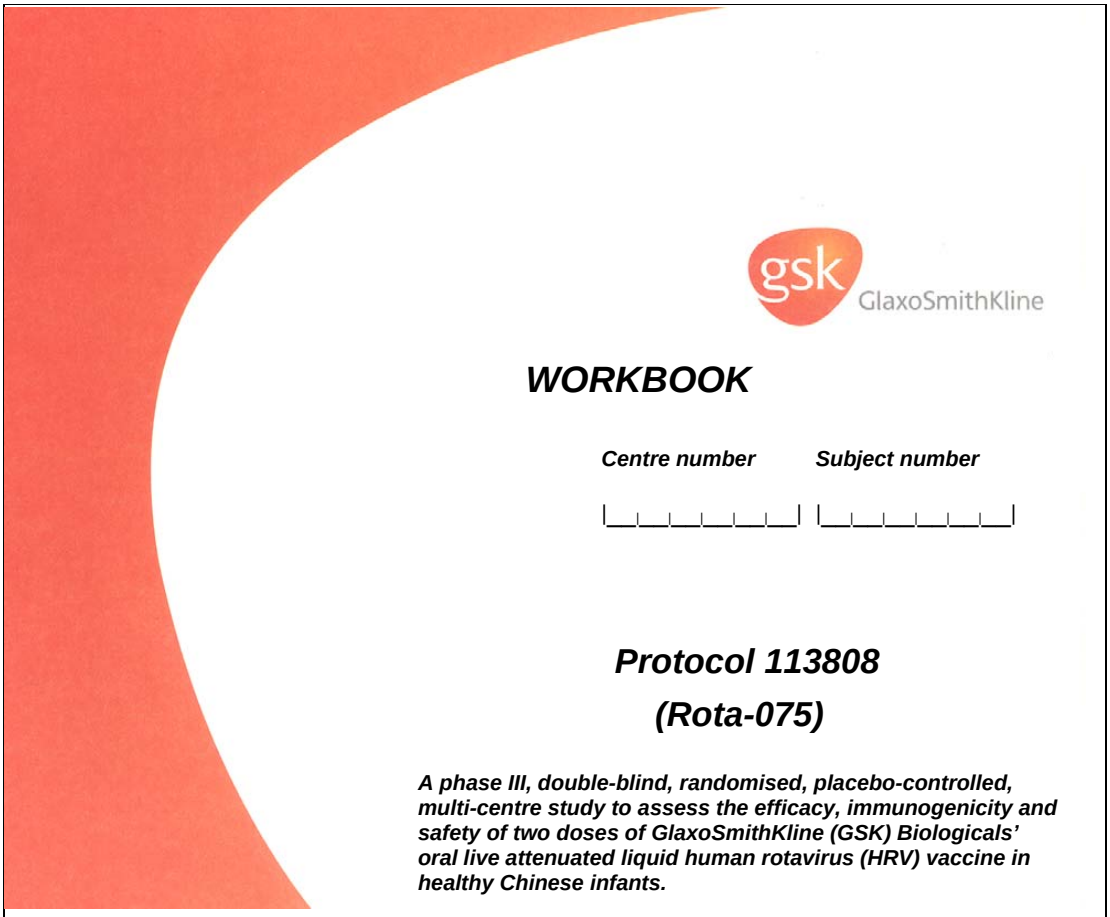

# *WORKBOOK*

***Centre number*** ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

## *Protocol 113808*
## *(Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted]

## GENERAL INSTRUCTIONS

**ABBREVIATIONS**
Abbreviations for medical conditions, clinical events or drug names are to be avoided.

**DATES**
Use the following 3-letter abbreviations to indicate months:

| | | |
|---|---|---|
| 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**|**8**| = 1st January 2008

**MISSING DATA CODES**
Preferably use following codes:

ND = Not Done
NA = Not Applicable
NK = Not Known

For all subjects participating to an epoch (or to a study if only one epoch), the **End of epoch** (or the Study Conclusion if only one epoch) and the corresponding **Medication, Concomitant Vaccination, (S)AE sections** must be completed.

If a subject doesn't participate to an epoch (or to a study if only one epoch), neither the **End of epoch** (or the Study Conclusion if only one epoch) nor the corresponding **Medication, Concomitant Vaccination, (S)AE sections** have to be completed.

.

# ADVERSE EVENT DEFINITIONS

## INTENSITY FOR SOLICITED SYMPTOMS

**Solicited general adverse events for liquid HRV vaccine/placebo (excluding subjects in immunogenicity sub-cohort 2)**

***Fever :*** Record temperature in °C

***Irritability/Fussiness***
**0**: Behavior as usual
**1**: Mild: Crying more than usual / no effect on normal activity
**2**: Moderate: Crying more than usual / interferes with normal activity
3**:** Severe: Crying that cannot be comforted / prevents normal activity

***Loss of appetite***
**0**: Appetite as usual
**1**: Mild: Eating less than usual / no effect on normal activity
**2**: Moderate: Eating less than usual / interferes with normal activity
**3**: Severe: Not eating at all

***Cough/runny nose***
**0**: Normal
**1**: Mild: Cough/runny nose which is easily tolerated
**2**: Moderate: Cough/runny nose which interferes with daily activity
**3**: Severe: Cough/runny nose which prevents daily activity

***Diarrhea* :** Record the number of looser than normal stools /day

***Vomiting :*** Record the number of vomiting episodes/day

**Solicited adverse events for co-administered childhood vaccines**

***Pain***
**0**: None
**1**: Mild: Minor reaction to touch
**2**: Moderate: Cries/protests on touch
3**:** Severe: Cries when limb is moved/spontaneously painful

***Irritability/Fussiness***
**0**: Behavior as usual
**1**: Mild: Crying more than usual / no effect on normal activity
**2**: Moderate: Crying more than usual / interferes with normal activity
3**:** Severe: Crying that cannot be comforted / prevents normal activity

***Loss of appetite***
**0**: Appetite as usual
**1**: Mild: Eating less than usual / no effect on normal activity
**2**: Moderate: Eating less than usual / interferes with normal activity
**3**: Severe: Not eating at all

Redness at injection site: Record greatest surface diameter in mm

Swelling at injection site: Record greatest surface diameter in mm

***Drowsiness***
**0**: Behaviour as usual
**1**: Mild: Drowsiness easily tolerated
**2**: Moderate: Drowsiness that interferes with normal activity
**3:** Severe:Drowsiness that prevents normal activity

**Gastrointestinal symptoms (**nausea, vomiting, diarrhea and/or abdominal pain)

**0**: Gastrointestinal symptoms normal
**1**: Mild: Gastrointestinal symptoms that are easily tolerated
**2**: Moderate: Gastrointestinal symptoms that interfere with normal activity
**3:** Severe:Gastrointestinal symptoms that prevent normal activity

***Fever*** *:* Record temperature in °C

# ADVERSE EVENT DEFINITIONS

## INTENSITY FOR UNSOLICITED SYMPTOMS

**1: Mild:** An adverse event (AE) which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
**2: Moderate:** An AE which is sufficiently discomforting to interfere with normal everyday activities.
**3: Severe:** An AE which prevents normal, everyday activities
(In a young child, such an AE would, for example, prevent attendance at school/kindergarden/a day-care centre and would cause the parents/legally acceptable representatives 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: the 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: the 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: the AE is the cause of death (only applicable for serious adverse event reports)

## SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is any untoward medical occurrence that:
• results in death
• is life threatening
• results in persistent or significant disability / incapacity
• requires in-patient hospitalization
• requires prolongation of existing hospitalization
• is a congenital anomaly / birth defect in the offspring of a study subject
• In addition, important medical events that may not be immediately life-threatening or result in death or hospitalisation but that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above should also be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
For each SAE the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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**113808 (Rota-075)**

# OUTLINE OF STUDY PROCEDURES

**List of study procedures**

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | *Visit 7* |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | *Years* 1 of age | *April 2012*[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | *Efficacy follow up* |
| Informed consent | ● | | | | | | |
| *Re-consenting for Visit 7 follow-up* | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | O | O | O | O | O | O |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approxi-mately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 2) | ● (Approxima-tely 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+DTPa) | ● (OPV+DTPa) | ● (DTPa) | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of *unsolicited AEs* within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | O | O | O | O | O | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

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**113808 (Rota-075)**

# OUTLINE OF STUDY PROCEDURES

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
*[β] i.e. end of the RV season in China. Amended: 05 August 2011*

## Intervals between study visits

| Interval | Optimal length of interval [1] | Maximum interval allowed [2] |
|---|---|---|
| 1 (Visit 1)→(Visit 2) | 30-48 days | 21-48 days |
| 2 ((Visit 2)→(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3)→(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | *1 year of age±2 weeks[γ]* | *1 year of age ±30 days* |
| *6 (Visit 6) → (Visit 7)* | *01 April 2012 to 30 April 2012[γ]* | *01 April 2012 to 31 May 2012* |

[1]. Whenever possible the investigator should arrange study visits within this interval
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they make the study visit outside this interval
*[γ] It is a defined time point for follow up visit in a range and not an interval. Amended: 05 August 2011*
Note: The date of the previous visit serves as the reference date for intervals between study visits. Refer to section Error! Reference source not found. for details on the study visits applicable to the subjects in the study.

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**113808 (Rota-075)**

| | | | Centre Number | Subject Number |
|---|---|---|---|---|
| | | | \|__\|__\|__\|__\|__\|__\| | \|__\|__\|__\|__\|__\|__\| |

# DEMOGRAPHICS

**Date of Birth:** |__|__| |__|__|__| |__|__|__|__|
day month year

**Gender:**

[M] ☐ Male
[F] ☐ Female

**Geographic Ancestry:**

[91] ☐ Asian – Chinese Heritage
[99] ☐ Other, specify: _____

## SUBJECT SUB-COHORT

Please specify sub-cohort:

☐ Immunogenicity sub-cohort 1
☐ Immunogenicity sub-cohort 2
☐ Non Immunogenicity cohort

1

**VISIT 1**

**DAY 0**

# Informed Consent has to be obtained prior to any study procedure

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year | \|__\|__\|__\|__\|__\|__\| |

# INFORMED CONSENT

*I certify that Informed Consent has been obtained prior to any study procedure.*

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Did the subject agree that her/his biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the study vaccine(s)/product(s) or the disease(s) under study? [type 4 tests]

☐ Yes ☐ No ☐ NA

2

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **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 of the 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 parent(s)/Legally Acceptable Representative(s) (LAR) can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).

[2] ☐ A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.

[3] ☐ Written informed consent obtained from the parent(s)/LAR of the subject.

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ Born after a gestation period of 36 to 42 weeks inclusive.

## EXCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Child in care.

- Please refer to the GLOSSARY OF TERMS for the definition of child in care.

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

[8] ☐ Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone 0.5 mg/kg/day, or equivalent, inhaled and topical steroids are allowed.

[9] ☐ Planned administration/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.of the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.

[10] ☐ 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).

[11] ☐ Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

3

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | | \|__\|__\|__\|__\|__\|__\| |

# ELIGIBILITY CHECK – continued

## EXCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[ 12 ] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

[ 13 ] ☐ Family history of congenital or hereditary immunodeficiency.

[ 14 ] ☐ History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.

[ 15 ] ☐ Major congenital defects or serious chronic illness.

[ 16 ] ☐ History of confirmed RV GE.

[ 17 ] ☐ Acute disease and/or fever at the time of enrolment.

- Fever is defined as temperature (37.1°C on axillary setting as defined by the Chinese authorities.
- Subjects with a minor illness (such as mild diarrhea mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).

[ 18 ] ☐ GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).

[ 19 ] ☐ Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

**In addition to the criteria mentioned above, the following criteria will be applicable to all subjects in the immunogenicity sub-cohort 2:**

[ 20 ] ☐ History of diphtheria, tetanus and pertussis disease.

[ 21 ] ☐ History of seizures or progressive neurological disease.

[ 22 ] ☐ Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | | \|__\|__\|__\|__\|__\|__\| |

# GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions, signs or symptoms present prior to the start of the study?

☐ No ☐ Yes → Please give diagnosis and tick (✓) appropriate Past/Current box(es).

| MedDRA SYSTEM ORGAN CLASS | DIAGNOSIS | PAST | CURRENT |
|---|---|---|---|
| [1] **Skin and subcutaneous tissue** | _____ | ☐ | ☐ |
| | _____ | ☐ | ☐ |
| [2] **Musculoskeletal and connective tissue** | _____ | ☐ | ☐ |
| | _____ | ☐ | ☐ |
| [3] **Cardiac** | _____ | ☐ | ☐ |
| [4] **Vascular** | _____ | ☐ | ☐ |
| [5] **Respiratory, thoracic and mediastinal** | _____ | ☐ | ☐ |
| | _____ | ☐ | ☐ |
| [6] **Gastrointestinal** | _____ | ☐ | ☐ |
| [7] **Hepatobiliary** | _____ | ☐ | ☐ |
| [8] **Renal and urinary** | _____ | ☐ | ☐ |
| [9] **Nervous system** | _____ | ☐ | ☐ |
| [10] **Eye** | _____ | ☐ | ☐ |
| [11] **Ear and labyrinth** | _____ | ☐ | ☐ |
| [12] **Endocrine** | _____ | ☐ | ☐ |
| [13] **Metabolism and nutrition** | _____ | ☐ | ☐ |
| [14] **Blood and lymphatic system** | _____ | ☐ | ☐ |
| [15] **Immune system** (incl allergies, autoimmune disorders) | _____ | ☐ | ☐ |
| | _____ | ☐ | ☐ |
| [16] **Infections and infestations** | _____ | ☐ | ☐ |
| [17] **Neoplasms benign, malignant and unspecified** (incl cysts, polyps) | _____ | ☐ | ☐ |
| | _____ | ☐ | ☐ |
| [18] **Surgical and medical procedures** | _____ | ☐ | ☐ |
| [99] **Other** | _____ | ☐ | ☐ |
| | _____ | ☐ | ☐ |

Please report medication(s) as specified in the Epoch and fill in the **Medication** section.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | | \|__\|__\|__\|__\|__\|__\| |

## VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

Gestational age |__|__|.|__| weeks

## LABORATORY TESTS (Only for Immunogenicity sub-cohort 1 and 2)

**SERUM SAMPLE** [SER]
(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Clearstone Accession Number *: |__|__|__|__|__|__|__|__|__|__|

☐ No

* **Please prefix Clearstone Accession Number with "C"**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | **Immunogenicity Sub-cohort 1 and Non Immunogenicity cohort** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|.|__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|. |__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

Has **OPV Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

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CONFIDENTIAL

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## VACCINE ADMINISTRATION (continued)

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:

[I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **DOSE 1** | | _____ |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 7?

[N] ☐ No
[Y] ☐ Yes, please tick No/Yes for each sign/symptom and complete further as necessary.
[U] ☐ Unknown, no information available
[NA] ☐ Not applicable, no vaccine administered.

Record temperatures if during the solicited period at least one oral/axillary/tympanic measure is above or equal to 37.1 °C or at least one rectal (or tympanic-rectal conversion) measure is above or equal to 37.6°C.

| **Temperature [TE]**<br>≥ 37.1 °C [A/O/T/TO]<br>≥ 37.6 °C [R/TR]<br>☐ No<br>☐ Yes → °C<br>☐ Not Taken | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **After Day 7**<br>If ongoing, record **maximum temperature** and **end date** | | | **Rel. to inv. Product** | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | __._ | __._ | __._ | __._ | __._ | __._ | __._ | __._ | Ongoing | **Max** Temp. | ✓ box if continuing at end of study ↓ | | |
| | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ No<br>☐ Yes → | ___._ | __ __ __ __ __ __ __ __ __ __ __ __ or ☐ | ☐ No<br>☐ Yes | NO/HO/ER/MD<br>__ __ |

Route: [A] ☐ Axillary (armpit) (Preferred)
[O] ☐ Oral
[R] ☐ Rectal
[T] ☐ Tympanic
↳ conversion:
[T] ☐ none (or unknown)
[TO] ☐ oral conversion
[TR] ☐ rectal conversion

| **Intensity**: 0 / 1 / 2 / 3<br>*(see Adverse Events definitions)* | **Relationship to investigational product**:<br>Is there a reasonable possibility that the AE may have been caused by the investigational product. | **Medically attended visit**:<br>*(see protocol for full definition)*<br>NO: None<br>HO: Hospitalization<br>ER: Emergency Room<br>MD: Medical Personnel |
|---|---|---|

If any of these adverse events meets the definition of **serious**, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **DOSE 1** | **Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (continued)

| General sign / symptom | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day6 | Day7 | After Day 7: Ongoing | After Day 7: Max intensity | After Day 7: Date of last day of sign/symptoms day month year | Rel. to inv. Product | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/Fussiness** [IR] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Cough/runny nose** [CO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Diarrhea** [DA] ☐ No ☐ Yes → Record the number of looser than normal stools /day | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Vomiting** [VO] ☐ No ☐ Yes → Record the number of vomiting episodes/day | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |

**Intensity:**
0 / 1 / 2 / 3
*see Adverse Events definitions)*

**Relationship to investigational product:**
Is there a reasonable possibility that the AE may have been caused by the investigational product.

**Medically attended visit:** *(see protocol for full definition)*
NO: None ER: Emergency Room
HO: Hospitalization MD: Medical Personnel

**Stool sample should be collected in case of diarrhea according to protocol which is 3 or more looser than normal stools per day**

**Stool Collection:** Stool collection date: |__| |___| |_____| hour: |__| min: |__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|

Stool collection date: |__| |___| |_____| hour: |__| min: |__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|

**If diarrhea, please complete the following items:**

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify: _____

**(*) Please prefix Clearstone Accession Number with "C"**

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **DOSE 1** | **Immunogenicity Sub-cohort 2** | __\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (continued)

| General sign / symptom | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day6 | Day7 | After Day 7: Ongoing | After Day 7: Max intensity | After Day 7: Date of last day of sign/symptoms day month year | Rel. to inv. Product | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness** [IR] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __\|__\|__\|__\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD _\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __\|__\|__\|__\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD _\|_\| |
| **Drowsiness** [DR] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __\|__\|__\|__\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD _\|_\| |
| **Gastrointestinal symptoms** † [GI] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __\|__\|__\|__\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD _\|_\| |

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain.

| **Intensity:** | **Relationship to investigational product:** | **Medically attended visit:** *(see protocol for full definition)* | | | |
|---|---|---|---|---|---|
| 0 / 1 / 2 / 3 | Is there a reasonable possibility that the AE may have been caused | NO: | None | ER: | Emergency Room |
| *see Adverse Events definitions)* | by the investigational product. | HO: | Hospitalization | MD: | Medical Personnel |

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours**.

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**VISIT 2**

**MONTH 1**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | | \|__\|__\|__\|__\|__\|__\| |

## CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or Solicited AE Code |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | ___ ___ ____ (day month year) | _____ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 1 AND NON-IMMUNOGENICITY SUB-COHORT**

Did the subject present GE from Day 8 after Dose 1 of HRV vaccine or Placebo until Visit 2?

OR

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 1 to Visit 2?

☐ No

☐ Yes, If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|. |__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: ----------

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vaccine intake after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__| or solicited AE code |__|__|

[OTH] ☐ Other, please specify: ----------

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|. |__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [To] ☐ oral conversion
    - [Tr] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: ----------

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

Has **OPV Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: ----------

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION (continued)

Has **DTPa Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number: \|__\|__\|__\|__\|__\|__\|

→ Injection Site / Side / Route:

☐ According to protocol: Anterolateral Thigh - Left - IM

☐ Not according to protocol,

specify Site: [1] ☐ Deltoid [3] ☐ Thigh [6] ☐ Buttock

Side: [L] ☐ Left [R] ☐ Right

Route: [IM] ☐ I.M. [SC] ☐ S.C.

→ *if relevant*, comment on administration: _____

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. \|__\|__\|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. \|__\|__\| or solicited AE code \|__\|__\|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS

### DTPa vaccine injection site

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 7?

[N] ☐ No
[Y] ☐ Yes, please tick No/Yes for each sign/symptom and complete further as necessary.
[U] ☐ Unknown, no information available
[NA] ☐ Not applicable, no vaccine administered.

| **Local sign / symptom** | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day6** | **Day7** | **After Day 7** Ongoing | Max Intensity/ Size | Date of last day of sign/symptoms day month year | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Redness** [RE] ☐ No ☐ Yes → size (mm): | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | NO/HO/ER/MD \|_\|_\| |
| **Swelling** [SW] ☐ No ☐ Yes → size (mm): | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | NO/HO/ER/MD \|_\|_\| |
| **Pain** [PA] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | NO/HO/ER/MD \|_\|_\| |

**Intensity:**
0 / 1 / 2 / 3
*see Adverse Events definitions)*

**Medically attended visit:** *(see protocol for full definition)*
NO: None ER: Emergency Room
HO: Hospitalization MD: Medical Personnel

If any of these adverse events meets the definition of **serious**, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | | _____ |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 7?

[N] ☐ No
[Y] ☐ Yes, please tick No/Yes for each sign/symptom and complete further as necessary.
[U] ☐ Unknown, no information available
[NA] ☐ Not applicable, no vaccine administered.

Record temperatures if during the solicited period at least one oral/axillary/tympanic measure is above or equal to 37.1 °C or at least one rectal (or tympanic-rectal conversion) measure is above or equal to 37.6°C.

| **Temperature [TE]**<br>≥ 37.1 °C [A/O/T/TO]<br>≥ 37.6 °C [R/TR]<br>☐ No<br>☐ Yes → °C<br>☐ Not Taken | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **After Day 7**<br>If ongoing, record **maximum temperature** and **end date** | | | **Rel. to inv. Product** | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | __._ ☐ Not Taken | __._ ☐ Not Taken | __._ ☐ Not Taken | __._ ☐ Not Taken | __._ ☐ Not Taken | __._ ☐ Not Taken | __._ ☐ Not Taken | __._ ☐ Not Taken | Ongoing | **Max** Temp. | ✓ box if continuing at end of study ↓ | | |
| | | | | | | | | | ☐ No<br>☐ Yes → | ___._ | __ __ __ __ __ __ or ☐ | ☐ No<br>☐ Yes | NO/HO/ER/MD<br>__ __ |

Route: [A] ☐ Axillary (armpit) (Preferred)
[O] ☐ Oral
[R] ☐ Rectal
[T] ☐ Tympanic
↳ conversion:
[T] ☐ none (or unknown)
[TO] ☐ oral conversion
[TR] ☐ rectal conversion

| **Intensity**: 0 / 1 / 2 / 3<br>*(see Adverse Events definitions)* | **Relationship to investigational product**:<br>Is there a reasonable possibility that the AE may have been caused by the investigational product. | **Medically attended visit**:<br>*(see protocol for full definition)*<br>NO: None<br>HO: Hospitalization<br>ER: Emergency Room<br>MD: Medical Personnel |
|---|---|---|

If any of these adverse events meets the definition of **serious**, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (continued)

| General sign / symptom | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day6 | Day7 | After Day 7: Ongoing | After Day 7: Max intensity | After Day 7: Date of last day of sign/symptoms day month year | Rel. to inv. Product | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/Fussiness** [IR] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Cough/runny nose** [CO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Diarrhea** [DA] ☐ No ☐ Yes → Record the number of looser than normal stools /day | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Vomiting** [VO] ☐ No ☐ Yes → Record the number of vomiting episodes/day | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |

**Intensity**:
0 / 1 / 2 / 3
*see Adverse Events definitions)*

**Relationship to investigational product**:
Is there a reasonable possibility that the AE may have been caused by the investigational product.

**Medically attended visit**: *(see protocol for full definition)*
NO: None ER: Emergency Room
HO: Hospitalization MD: Medical Personnel

**Stool sample should be collected in case of diarrhea according to protocol which is 3 or more looser than normal stools per day**

**Stool Collection:** Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|__|

**If diarrhea, please complete the following items:**

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify: _____

**(*) Please prefix Clearstone Accession Number with "C"**

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.**

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**113808 (Rota-075)**

| | | | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

| **General sign / symptom** | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day6** | **Day7** | **After Day 7** Ongoing | Max intensity | Date of last day of sign/symptoms day month year | **Rel. to inv. Product** | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness** [IR] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Drowsiness** [DR] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Gastrointestinal symptoms** † [GI] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain. These AEs are specific to OPV.

| **Intensity:** | **Relationship to investigational product:** | **Medically attended visit:** *(see protocol for full definition)* | | | |
|---|---|---|---|---|---|
| 0 / 1 / 2 / 3 *see Adverse Events definitions)* | Is there a reasonable possibility that the AE may have been caused by the investigational product. | NO: | None | ER: | Emergency Room |
| | | HO: | Hospitalization | MD: | Medical Personnel |

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.**

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**VISIT 3**

**MONTH 2**

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

☐ [SAE] Serious adverse event:

→ Please complete and submit **SAE** report.

→ Please specify SAE Case No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section

→ Please specify AE No. |__|__| Or solicited AE code: |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [SST] Sponsor study termination.

☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | __ __ / __ __ __ / __ __ __ __<br>day month year | __ __ __ __ __ __ __ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 1 AND NON-IMMUNOGENICITY SUB-COHORT**

Did the subject present GE from Day 8 after Dose 2 of HRV vaccine or Placebo until Visit 3?

OR

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 2 to Visit 3?

☐ No

☐ Yes …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

## LABORATORY TESTS (only for subjects in Immunogenicity sub-cohort 1 and 2)

### SERUM SAMPLE [SER]

(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: __ __ / __ __ __ / __ __ __ __
day month year

→ Clearstone Accession Number *: __ __ __ __ __ __ __ __ __ __

☐ No

*** Please prefix Clearstone Accession Number with "C"**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|. |__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **OPV Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

Has **DTPa Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number: |__|__|__|__|__|__|

→ Injection Site / Side / Route:

☐ According to protocol: Anterolateral Thigh - Left - IM

☐ Not according to protocol,
specify Site: [1] ☐ Deltoid [3] ☐ Thigh [6] ☐ Buttock
Side: [L] ☐ Left [R] ☐ Right
Route: [IM] ☐ I.M. [SC] ☐ S.C.

→ *if relevant*, comment on administration: _____

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION (continued)

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__| Or solicited AE code: |__|__|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

**Note: Please report any non-serious AE that lead to withdrawal**

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**VISIT 4**

**MONTH 3**

## Only for subjects in sub-cohort 2

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 4** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or solicited AE code: |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 4** | __ __ day __ __ month __ __ __ __ year | __ __ __ __ __ __ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 3 to Visit 4?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 4** | | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
(if different from visit date) day month year

Pre-Vaccination temperature: \|__\|__\|. \|__\| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **DTPa Vaccine** been co-administered?

- [N] ☐ No → Please give reason below.
- [Y] ☐ Yes → Administered Treatment Number: \|__\|__\|__\|__\|__\|__\|
  - → Injection Site / Side / Route:
    - ☐ According to protocol: Anterolateral Thigh - Left - IM
    - ☐ Not according to protocol,
      specify Site: [1] ☐ Deltoid [3] ☐ Thigh [6] ☐ Buttock
      Side: [L] ☐ Left [R] ☐ Right
      Route: [IM] ☐ I.M. [SC] ☐ S.C.
  - → *if relevant*, comment on administration: _____

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

- [SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report
  - → Please specify SAE Case No. \|__\|__\|
- [AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section
  - → Please specify AE No. \|__\|__\| Or solicited AE code: \|__\|__\|
- [OTH] ☐ Other, please specify: _____
  (e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

**Note: Please report any non-serious AE that lead to withdrawal**

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**VISIT 5**

**MONTH 4**

## Only for subjects in sub-cohort 2

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 5** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or solicited AE code: |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 5** | __ __ (day) __ __ __ (month) __ __ __ __ (year) | __ __ __ __ __ __ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 4 to Visit 5?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

## LABORATORY TESTS

**SERUM SAMPLE** [SER]
(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: __ __ (day) __ __ __ (month) __ __ __ __ (year)

→ Clearstone Accession Number *: __ __ __ __ __ __ __ __ __ __

☐ No

*** Please prefix Clearstone Accession Number with "C"**

**Note: Please report any non-serious AE that lead to withdrawal**

**VISIT 6**

**YEAR 1 OF AGE**

**EFFICACY**

**FOLLOW-UP**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 6** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for the visit 6?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or solicited AE code: |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 6** | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year | \|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 1 AND NON-IMMUNOGENICITY SUB-COHORT**

Did the subject present GE between Visit 3 to visit 6?

OR

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 5 to Visit 6?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

## LABORATORY TESTS (only for immunogenicity sub-cohort 1 and 2)

### SERUM SAMPLE [SER]

(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Clearstone Accession Number *: |__|__|__|__|__|__|__|__|__|__|

☐ No

*** Please prefix Clearstone Accession Number with "C"**

**Note: Please report any non-serious AE that lead to withdrawal**

**POST VISIT 6**
**INFORMED CONSENT**

# An additional Informed Consent has to be obtained prior to any study procedure related to follow up period between visit 6 and visit 7

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **POST VISIT 6** | | \|__\|__\|__\|__\|__\|__\| |

## INFORMED CONSENT

Did the subject's parents/LAR sign the informed consent to participate in the follow up period between visit 6 and visit 7?

☐ No

☐ Yes → please fill the **informed consent date** \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

☐ NA

**Reminder:**

- 'Yes' should be answered if the Protocol Amendment 2 has been approved and the subject signed the informed consent to participate in the follow up period between visit 6 and visit 7.
- 'No' should be answered if the Protocol Amendment 2 has been approved and the subject did not sign the informed consent to participate in the follow up period between visit 6 and visit 7.
- 'NA' should be answered if the Protocol Amendment was not approved.

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**VISIT 7**

**EFFICACY**

**FOLLOW-UP**

**Only for subjects whose parents//LAR have signed the Informed Consent to participate in the follow up period between visit 6 and visit 7**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 7** | | \|__\|__\|__\|__\|__\|__\| |

## CHECK FOR STUDY CONTINUATION

Did the subject return for the visit 7?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or solicited AE code: |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 7** | _____ _____ _____<br>day month year | _____ |

## GASTROENTERITIS EPISODES

**FOR ALL COHORTS**

Did the subject present GE from Visit 6 to Visit 7?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

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# GASTROENTERITIS EPISODES VISIT 1 TO VISIT 7

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**113808 (Rota-075)**

| | | | | |
|---|---|---|---|---|
| | | | | Subject Number |
| | | | | \|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 7

**EPISODE N°**: |__|__|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C)** → **route:** | ☐ **Axillary** (**)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

**(*) Please prefix Clearstone Accession Number with "C"**

**(**) Route: axillary is mandatory.**

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**113808 (Rota-075)**

| | | | | Subject Number |
|---|---|---|---|---|
| | | | | \|__\|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 7

**EPISODE N°**: |__|__|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|__|

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C)** → **route:** | ☐ **Axillary** (**)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |

**(*) Please prefix Clearstone Accession Number with "C"**

(**) **Route: axillary is mandatory.**

CONFIDENTIAL

113808 (Rota-075)

| | | | | Subject Number |
|---|---|---|---|---|
| | | | | \|__\|__\|__\|__\|__\|__\| |

# GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 7

**EPISODE N°**: |__|__|

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C)** → **route:** | ☐ **Axillary** (**)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|_\|_\| \|_\|_\|_\| \|_\|_\|_\|_\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

**(*) Please prefix Clearstone Accession Number with “C”**

**(**) Route: axillary is mandatory.**

**CONCOMITANT VACCINATION VISIT 1 TO VISIT 7**

CONFIDENTIAL

**113808 (Rota-075)**

| | | | | |
|---|---|---|---|---|
| | | Visit | | Subject Number |
| | | **CONCOMITANT VACCINATION** | | \|__\|__\|__\|__\|__\|__\| |
| | | | | |

# CONCOMITANT VACCINATION

Have any vaccines other than the study vaccine(s) been administered during the time frame as specified in the protocol?

☐ No

☐ Yes → Please complete the following table.

| **Trade / (Generic) Name** | **Route** | **Administration date**<br>**day month year** |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |

**Route:**

| | | | |
|---|---|---|---|
| ID | = Intradermal | PE | = Parenteral |
| IH | = Inhalation | PO | = Oral |
| IM | = Intramuscular | SC | = Subcutaneous |
| IN | = Intranasal | SL | = Sublingual |
| IV | = Intravenous | TD | = Transdermal |
| OTH | = Other | UNK | = Unknown |

***Previous vaccination against DTPa and OPV should be reported in the CRF***

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# MEDICATION
# VISIT 1 TO VISIT 7

**ROUTE**

| Code | Label |
|---|---|
| ID | Intradermal |
| IH | Inhalation |
| IM | Intramuscular |
| IN | Intranasal |
| IR | Intraarticular |
| IV | Intravenous |
| PE | Parenteral |
| PO | Oral |
| PR | Rectal |
| SC | Subcutaneous |
| SL | Sublingual |
| TD | Transdermal |
| TO | Topical |
| VA | Vaginal |
| OTH | Other |
| UNK | Unknown |

| | | | | |
|---|---|---|---|---|
| | | Visit | | Subject Number |
| | | **MEDICATION** | | \|__\|__\|__\|__\|__\|__\| |

# MEDICATION

Have any medications been administered during the time frame as specified in the protocol?

☐ No
☐ Yes → Please complete the following table.

| **Trade / Generic Name** | **Medical Indication** | **Total daily dose**<br>**Dose** | <br>**Unit** | **Route**<br>Use codes given on pre bvious page | **Start Date**day/month/year<br>**End Date**day/month/year<br>or ✓ box if continuing at end of study ↓ |
|---|---|---|---|---|---|
| <br>For GSK use only | ☐ in anticipation of study vaccine reaction<br>☐ chronic use | | | | Start: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|<br>End: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ |
| <br>For GSK use only | ☐ in anticipation of study vaccine reaction<br>☐ chronic use | | | | Start: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|<br>End: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ |
| <br>For GSK use only | ☐ in anticipation of study vaccine reaction<br>☐ chronic use | | | | Start: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|<br>End: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ |
| <br>For GSK use only | ☐ in anticipation of study vaccine reaction<br>☐ chronic use | | | | Start: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|<br>End: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ |
| <br>For GSK use only | ☐ in anticipation of study vaccine reaction<br>☐ chronic use | | | | Start: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|<br>End: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ |
| <br>For GSK use only | ☐ in anticipation of study vaccine reaction<br>☐ chronic use | | | | Start: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\|<br>End: \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ |

**NON-SERIOUS ADVERSE EVENT VISIT 1 TO VISIT 7**

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL** | **Immunogenicity sub-cohort 1 and Non-immunogenicity cohort** | \|__\|__\|__\|__\|__\|__\| |

## NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS

**(Please report *serious* adverse events only in the Serious Adverse Event report, not here)**

Have any non-serious adverse events/intercurrent medical conditions occurred during the time frame as specified in the protocol?

☐ No
☐ Yes → Please complete the following table.

| # | Event | Start date<br>Tick (✓) if 30 min immediate post-vaccination ↓ | | Outcome | End date | Maximum intensity | Relationship to investigational product(s) | Medically attended visit |
|---|---|---|---|---|---|---|---|---|
| | Diagnosis only (if known), otherwise sign / symptom | Day Month Year (DD MMM YYYY) | 30min post vacc | 1: Recovered/ Resolved<br>2: Recovering / Resolving<br>3: Not recovered/ Not resolved<br>4: Recovered/ Resolved with sequelae | Day Month Year (DD MMM YYYY) | 1: Mild<br>2: Moderate<br>3: Severe | Is there a reasonable possibility that the AE may have been caused by the investigational product?<br>Y=Yes N=No | **NO**:None<br>**HO**: Hospitalisation<br>**ER**: Emergency Room<br>**MD**:Medical Personnel<br>Refer to protocol for full definition |
| 1 | For GSK use only | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 2 | For GSK use only | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 3 | For GSK use only | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL** | **Immunogenicity sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS

**(Please report *serious* adverse events only in the Serious Adverse Event report, not here)**

Have any non-serious adverse events/intercurrent medical conditions occurred during the time frame as specified in the protocol?

☐ No
☐ Yes → Please complete the following table.

| # | Event | Site | Start date<br>Tick (✓) if 30 min immediate post-vaccination ↓ | | Outcome | End date | Maximum intensity | Relationship to investigational product(s) | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|
| | Diagnosis only (if known), otherwise sign / symptom | | Day Month Year (DD MMM YYYY) | 30min post vacc | 1: Recovered/ Resolved<br>2: Recovering / Resolving<br>3: Not recovered/ Not resolved<br>4: Recovered/ Resolved with sequelae | Day Month Year (DD MMM YYYY) | 1: Mild<br>2: Moderate<br>3: Severe | Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No | **NO**:None<br>**HO**: Hospitalisation<br>**ER**: Emergency Room<br>**MD**:Medical Personnel<br>Refer to protocol for full definition |
| 1 | For GSK use only | ☐ Non-Administration site<br>☐ Administration site | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 2 | For GSK use only | ☐ Non-Administration site<br>☐ Administration site | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 3 | For GSK use only | ☐ Non-Administration site<br>☐ Administration site | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |

**STUDY CONCLUSION**

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **STUDY CONCLUSION** | | \|__\|__\|__\|__\|__\|__\| |

# STUDY CONCLUSION

## LAST INFORMATION

Date of last contact or

date when the last information was collected on the subject's condition: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Was the subject in good condition at this date?

☐ Yes

☐ No → Give details in serious or non-serious adverse events section.

## OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event since the start of the study?

☐ No

☐ Yes → Check SAE report(s) have been submitted

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **CONCLUSION** | | \|__\|__\|__\|__\|__\|__\| |

## 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: _____

GlaxoSmithKline

**113808 [ROTA-075]**

| | | | Centre No. | UHS form version |
|---|---|---|---|---|
| | | | \|__\|__\|__\|__\|__\|__\|__\| | \|__\| |

## USE OF HUMAN SAMPLES BY GSK

**In addition to the tests described in the study protocol, please check what may also be done with the subject samples as per the Informed Consent Form (ICF) in use at your center.**

☐ Yes ☐ No [type 3a tests] Use of samples to improve, develop or assess tests related to the disease(s) or the vaccine(s)/product(s) under study that will allow more reliable measurement of the vaccine/product response. This excludes testing related to genes' hereditary characteristics and HIV

☐ Yes ☐ No [type 3b tests] ***With the prior permission of the institution independent Ethics Committee / Institutional Review Board:***

Use of samples to improve, develop or assess tests related to the disease(s) or the vaccine(s)/product(s) under study that will allow more reliable measurement of the vaccine/product response. This excludes testing related to genes' hereditary characteristics and HIV

☐ Yes ☐ No [type 4 tests] ***With the prior permission of the subject:***

Further research by GSK Biologicals that is NOT RELATED to the disease(s) or the vaccine(s)/product(s) under study. This research is done on an anonymous basis (any identification linking the subject to the sample is destroyed), excludes testing related to genes' hereditary characteristics and HIV, and does not affect the subject participation in the study.

**Please check GSK Biologicals sample storage period specified in the ICF in use at your center.**

☐ up to 15 years

☐ Other, specify: _____

**If new version of UHS:**

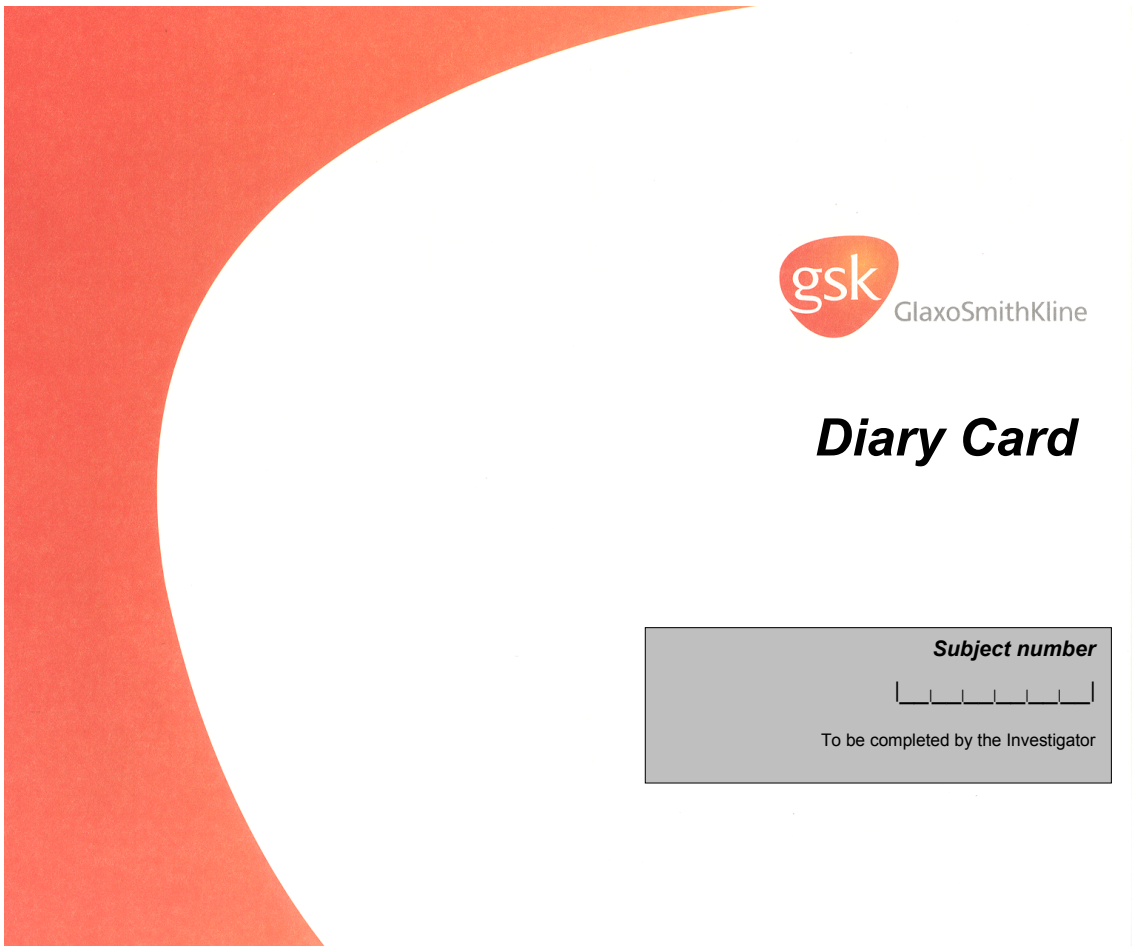
Date at which the new ICF version was first signed by a subject : |__|__| |__|__|__| |__|__|__|__|
day month year

Complete and submit a *new Use of Human Samples by GSK* form for each change in the ICF that affects the use of samples.

## INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__||__|__|__||__|__|__|__|
day month year

Printed Investigator's name: _____



GlaxoSmithKline

# Diary Card

**Subject number**

|__|__|__|__|__|__|__|

To be completed by the Investigator

## Protocol 113808
## (Rota-075)

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

Diary Card template13.1 – August 06, 2010

# VISIT 1

## Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort

Diary Card template13.1 – August 06, 2010

CONFIDENTIAL

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 1** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: ≥37.1°C Axillary | After Day 7: Max Temperature | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No<br>☐ Yes → | °C | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement:
(The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: Ongoing | After Day 7: Max Intensity | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Cough/runny nose → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**: Normal **1**: Cough/runny nose which is easily tolerated **2**: Cough/runny nose which interferes with daily activity **3**:Cough/runny nose which prevents daily activity | | | | | | | | | | | | | |
| **Diarrhea→** | | | | | | | | | ☐ No<br>☐ Yes → | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Record the number of looser than normal stools /day | | | | | | | | | | | | | |
| **Vomiting →** | | | | | | | | | ☐ No<br>☐ Yes → | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Record the number of vomiting episodes/day | | | | | | | | | | | | | |

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**Stool Collection:** Stool collection date: \|__\|___\|____\| hour: \|__\| min: \|__\|

Stool collection date: \|__\|___\|____\| hour: \|__\| min: \|__\|

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify:

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| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 1** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |

**Route:**

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IN = Intranasal
IV = Intravenous
OTH = Other

PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

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CONFIDENTIAL

| 113808 (Rota-075) | **DIARY CARD** **Visit 1** | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| Illness/Sign/Symptom | Max Intensity 1/2/3 | Start Date | End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

……

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

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# VISIT 2

Diary Card template 13.1 – August 06, 2010

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7 ≥37.1°C Axillary | After Day 7 Max Temperature | After Day 7 End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No<br>☐ Yes → | °C | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement: (The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7 Ongoing | After Day 7 Max Intensity | After Day 7 End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Cough/runny nose → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**: Normal **1**: Cough/runny nose which is easily tolerated **2**: Cough/runny nose which interferes with daily activity **3**:Cough/runny nose which prevents daily activity | | | | | | | | | | | | | |
| **Diarrhea→** | | | | | | | | | ☐ No<br>☐ Yes → | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Record the number of looser than normal stools /day | | | | | | | | | | | | | |
| **Vomiting →** | | | | | | | | | ☐ No<br>☐ Yes → | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Record the number of vomiting episodes/day | | | | | | | | | | | | | |

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**Stool Collection:** Stool collection date: \|__\|___\|____\| hour: \|__\| min: \|__\|

Stool collection date: \|__\|___\|____\| hour: \|__\| min: \|__\|

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify:

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| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |

**Route:**

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IN = Intranasal
IV = Intravenous
OTH = Other

PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

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| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| Illness/Sign/Symptom | Max Intensity 1/2/3 | Start Date | End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

……

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
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## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

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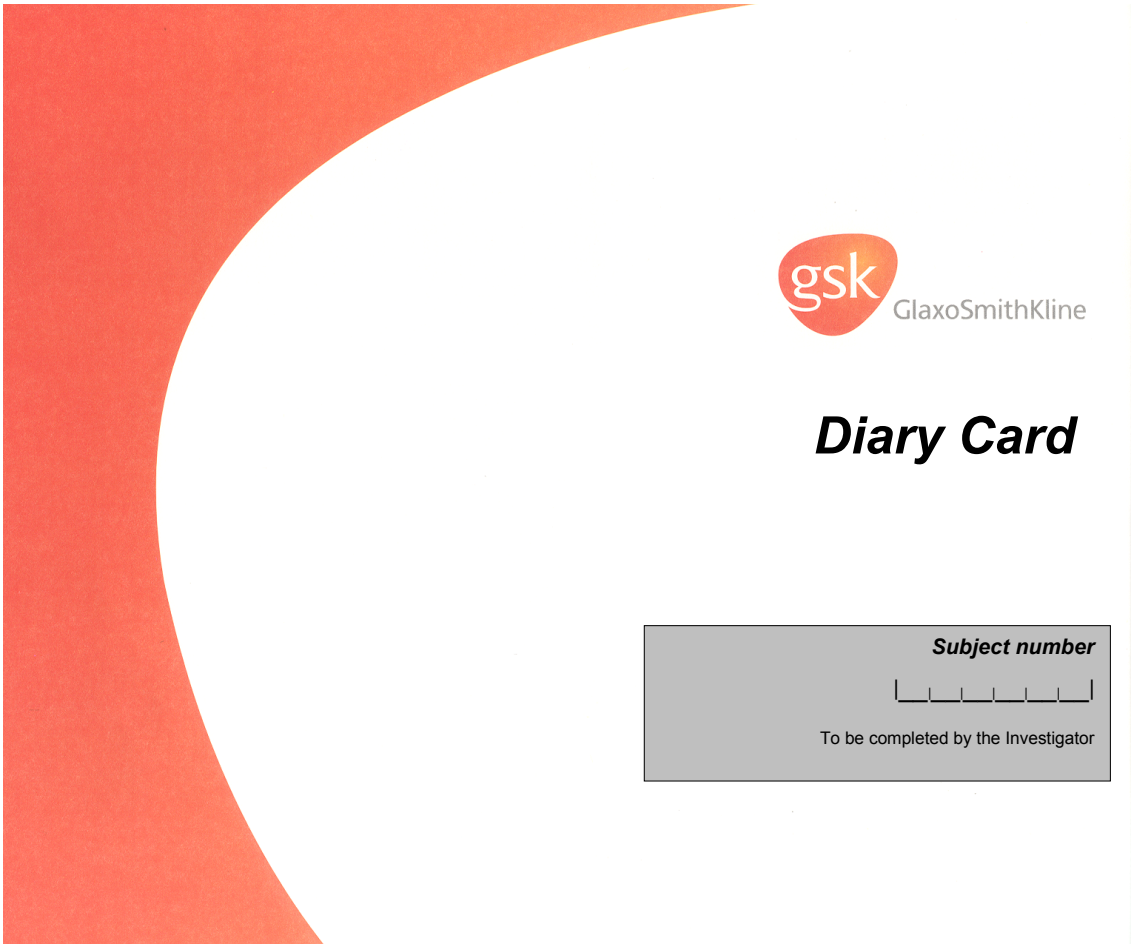


# Diary Card

***Subject number***

|__|__|__|__|__|__|__|

To be completed by the Investigator

## *Protocol 113808*
## *(Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

Diary Card template13.1 – August 06, 2010

# VISIT 1

**Immunogenicity Sub-Cohort 2**

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| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 1** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: ≥37.1°C Axillary | After Day 7: Max Temperature | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No<br>☐ Yes → | °C | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement:
(The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: Ongoing | After Day 7: Max Intensity | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Drowsiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: 0:Behaviour as usual 1: Mild: Drowsiness easily tolerated 2: Moderate: Drowsiness that interferes with normal activityactivity 3: Severe:Drowsiness that prevents normal activity | | | | | | | | | | | | | |
| **Gastrointestinal symptoms †→ intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\| |
| Intensity: 0: Gastrointestinal symptoms normal 1: Mild: Gastrointestinal symptoms that are easily tolerated 2: Moderate: Gastrointestinal symptoms that interfere with normal activity 3: Severe:Gastrointestinal symptoms that prevent normal activity | | | | | | | | | | | | | |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

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| 113808 (Rota-075) | **DIARY CARD** **Visit 1** | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| Illness/Sign/Symptom | Max Intensity 1/2/3 | Start Date | End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|
| | | | | ☐ No ☐ Yes | HO/ER/MD ___ |
| | | | | ☐ No ☐ Yes | HO/ER/MD ___ |
| | | | | ☐ No ☐ Yes | HO/ER/MD ___ |
| | | | | ☐ No ☐ Yes | HO/ER/MD ___ |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

……

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

# VISIT 2

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD** Visit 2 | **Subject Number** \|__\|__\|__\|__\|__\|__\|__\|__\| To be completed by the investigator |
|---|---|---|

## LOCAL SYMPTOMS
## DTPa Vaccine

To be completed by the investigator:

**Date of vaccination = Day 0**: _____ **Injection Site**: _____ **Side**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7 Ongoing | After Day 7 Max Intensity | After Day 7 End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Injection site **Redness** → size (mm) | mm | mm | mm | mm | mm | mm | mm | mm | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊_⌊_⌋ |
| Measure and record the greatest diameter (in mm). | | | | | | | | | | | | | |
| Injection site **Swelling** → size (mm) | mm | mm | mm | mm | mm | mm | mm | mm | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊_⌊_⌋ |
| Measure and record the greatest diameter (in mm). | | | | | | | | | | | | | |
| Injection site **Pain** → intensity (0/1/2/3) | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊_⌊_⌋ |
| Intensity: **0**:Absent **1**:Minor reaction to touch **2**:Cries/protests on touch **3**:Cries when limb is moved / spontaneously painful | | | | | | | | | | | | | |

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD** Visit 2 | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS (OPV + DTPa VACCINE)

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7 ≥37.1°C Axillary | After Day 7 Max Temperature | After Day 7 End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No ☐ Yes → | °C | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement: (The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7 Ongoing | After Day 7 Max Intensity | After Day 7 End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Drowsiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: 0:Behaviour as usual 1: Mild: Drowsiness easily tolerated 2: Moderate: Drowsiness that interferes with normal activityactivity 3: Severe:Drowsiness that prevents normal activity | | | | | | | | | | | | | |
| **Gastrointestinal symptoms †→ intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: 0: Gastrointestinal symptoms normal 1: Mild: Gastrointestinal symptoms that are easily tolerated 2: Moderate: Gastrointestinal symptoms that interfere with normal activity 3: Severe:Gastrointestinal symptoms that prevent normal activity | | | | | | | | | | | | | |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| **Illness/Sign/Symptom**<br>☑ if at vaccine injection site ↓ | **Max Intensity**<br>1/2/3 | **Start Date** | **End Date** | **Did you receive medical attention?*** | **Type of medical attention**<br>To be completed by the investigator |
|---|---|---|---|---|---|
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

.....

## MEDICATION

Record any medication taken since the last study vaccination.

| **Medication** | **Reason/Indication** | **Route**<br>To be completed by the investigator | **Dose and frequency** | **Start Date** | **End Date** |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010

# VISIT 3

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 3** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |

**Route:**

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IN = Intranasal
IV = Intravenous
OTH = Other

PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

Diary Card template13.1 – August 06, 2010

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 3** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | **Route** To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

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| |

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010

# VISIT 4

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 4** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |

**Route:**

| | | | |
|---|---|---|---|
| ID | = Intradermal | PE | = Parenteral |
| IH | = Inhalation | PO | = Oral |
| IM | = Intramuscular | SC | = Subcutaneous |
| IN | = Intranasal | SL | = Sublingual |
| IV | = Intravenous | TD | = Transdermal |
| OTH | = Other | UNK | = Unknown |

Diary Card template13.1 – August 06, 2010

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 4** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | **Route**<br>To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

| |
|---|
| |

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010


# *Gastroenteritis Diary Card*

***Subject number***

|__|__|__|__|__|__|__|

To be completed by the Investigator

## *Protocol 113808 (Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

Diary Card template13.1 – July 21, 2010

# For all Subjects who experience

# Gastroenteritis Episodes

CONFIDENTIAL

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms GE symptoms

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | |
|---|---|---|
| GlaxoSmithKline 113808<br>(Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms GE symptoms

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: __________________________

Medical advice:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | |
|---|---|---|
| 113808<br>(Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms GE symptoms

Treatment? ☐ No
☐ Yes →
☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

# List of Independent Ethics Committees /Institutional Review Boards

| Centre Number(s)* | Ethics Review Body | Location |
|---|---|---|
| [redacted] | [redacted] | [redacted]<br>Phone [redacted]<br>Email: [redacted] |

* GSK Biologicals assigned centre number

# Representative written information for patient and sample consent forms

Informed Consent Form for Efficacy subgroup

CONFIDENTIAL
113808 (ROTA-075)

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 01 (update with Version of Local ICF)**

**Date: 06 August 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease) and safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools

are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 2350 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she

is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit. |

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| Day | What will happen at this visit |
|---|---|
| | Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.
- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that**

**any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, 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. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. Preliminary data from a large post-marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31-day period following the first dose. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose.
These observations are limited to the first dose and not seen following administration of the second dose. Parents/guardians are asked to contact the study doctor if they noticed any signs and symptoms indicative and/or consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever).

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

GSK has identified the presence of material from Porcine circovirus-1 (PCV-1), a virus to which people are commonly exposed, in its Human Rotavirus Vaccine. There is no evidence that PCV-1 can infect humans or is harmful to humans. Based on these considerations and the extensive safety database available, the benefit/risk profile of GSK Biologicals' HRV vaccine has not changed and remains favourable.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this

study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Efficacy subgroup Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 01, 15 pages, dated 06 August 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Efficacy subgroup Subject ID_____

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I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian _____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent _____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness _____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 01 (update with Version of Local ICF)**

**Date: 06 August 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 600 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 3 millilitres)<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination. |

| **Day** | **What will happen at this visit** |
|---|---|
| | Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit.<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination.<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the

next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, 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. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. Preliminary data from a large post-marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31-day period following the first dose. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose.

These observations are limited to the first dose and not seen following administration of the second dose. Parents/guardians are asked to contact the study doctor if they noticed any signs and symptoms indicative and/or consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever).

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

GSK has identified the presence of material from Porcine circovirus-1 (PCV-1), a virus to which people are commonly exposed, in its Human Rotavirus Vaccine. There is no evidence that PCV-1 can infect humans or is harmful to humans. Based on these considerations and the extensive safety database available, the benefit/risk profile of GSK Biologicals' HRV vaccine has not changed and remains favourable.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from**

**samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 01, 15 pages, dated 06 August 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 01 (update with Version of Local ICF)**

**Date: 06 August 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 300 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she did not receive any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.
- He/she does not or has not had any history of diphtheria, tetanus and pertussis disease.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she does not have a disease that affects his/her nervous system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (Visit 6 = concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 2

**CONFIDENTIAL**
113808 (ROTA-075)

**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 4.5 millilitres)<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after Dose 1 of OPV vaccine<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>DTPa vaccine given on left thigh<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days |

| Day | What will happen at this visit |
|---|---|
| | (Days 0 – 7) after Dose 2 of OPV vaccine and Dose 1 of DTPa<br><br>Daily post-vaccination recording of solicited local adverse events within 8-days (Days 0 – 7) after Dose 1 of DTPa vaccine<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>Collection of blood sample (not more than 3 millilitres)<br><br>OPV vaccine given orally<br><br>DTPa vaccine given on left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br><br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 3 (Visit 4) | Return gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>DTPa vaccine injected on the left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and Visit 4)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 3 and Visit 4<br><br>Recording of any medical condition your child/ward has experienced between Visit 3 and Visit 4<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 4 (Visit 5) | Return gastroenteritis dairy cards given at previous visit |

| Day | What will happen at this visit |
|---|---|
| | Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 4 and Visit 5)<br>Recording of any medication/vaccination your child/ward has received between Visit 4 and Visit 5<br>Recording of any medical condition your child/ward has experienced between Visit 4 and Visit 5<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age (Visit 6) | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 5 till your child/ward is one year of age [Visit 6])<br>Recording of any medication/vaccination your child/ward has received between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of any medical condition your child/ward has experienced between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of serious adverse events<br>Study Conclusion |

- DTPa vaccine is a vaccine against diphtheria, tetanus and pertussis [whooping cough]) and OPV vaccine is a vaccine against polio.

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.

- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.

  – body (axillary) temperature.

  – solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- You will receive diary cards to record information of your child/ward on the following after the first two doses of the OPV vaccine and the first dose of the DTPa vaccine

  – body (axillary) temperature.

  - solicited (expected) general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) for DTPa and OPV vaccine and solicited (expected) local symptoms (pain, swelling, redness) for DTPa vaccine occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

- Your child/ward will also receive his/her routine childhood vaccinations recommended in China.

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, 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. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. Preliminary data from a large post-

marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31-day period following the first dose. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose.
These observations are limited to the first dose and not seen following administration of the second dose. Parents/guardians are asked to contact the study doctor if they noticed any signs and symptoms indicative and/or consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever).

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

GSK has identified the presence of material from Porcine circovirus-1 (PCV-1), a virus to which people are commonly exposed, in its Human Rotavirus Vaccine. There is no evidence that PCV-1 can infect humans or is harmful to humans. Based on these considerations and the extensive safety database available, the benefit/risk profile of GSK Biologicals' HRV vaccine has not changed and remains favourable.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

The following side effects may occur when your child/ward receives DTPa and OPV vaccines:

Like all medicines, DTPa can cause side effects, although not everybody gets them. Side effects that may occur are the following:

The following side effects related to study procedures may occur: (this may occur with up to more than 1 in 10 doses): irritability, sleepiness, redness and swelling at the injection site, fever (≥ 38.0°C).

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses): loss of appetite, restlessness, abnormal crying, diarrhoea, vomiting, itching, pain at the injection site.

The following side effects are less likely: (these may occur with up to 1 in 100 doses): headache, cough, bronchitis, rash, hard lump at the injection site, fatigue, fever (≥39.1°C)

The following side effects are rare: (these may occur 1 in 1000 doses of the vaccine): hives

The following side effects are very rare: (these may occur 1 in 10,000 doses of the vaccine):

As with all injectable vaccines, there is an extremely small risk of severe allergic reactions. These can be recognised by:

- Itchy rash of the hands and feet
- Swelling of the eyes and face
- Difficulty in breathing or swallowing.

These reactions will usually occur before leaving the doctor's surgery. However, if your child/ward gets any of these symptoms you should contact a doctor urgently.

- Swollen glands in the neck, armpit or groin
- Bleeding or bruising more easily than normal
- Collapse or periods of unconsciousness, lack of awareness, seizures or fits (with or without fever) which usually occur within 2 to 3 days after vaccination
- Temporarily stopping breathing
- Swelling of the entire injected limb

Like all medicines, OPV can cause side effects, although not everybody gets them. Side effects that may occur are the following:

Generally there are no adverse reactions after oral intake of OPV vaccine. The following side effects may occur in some subjects: fever, nausea, vomit, diarrhoea, and rashes. No special intervention is indicated generally, symptomatic treatment may be administered if necessary.

Vaccine associated paralytic poliomyelitis (VAPP) may be caused by inoculation of live attenuated poliomyelitis, and there is no exact statistical data domestically. VAPP incidence rates are 2-4 in one million, according to official statistical report by World Health Organization.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgments made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.

- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 01, 17 pages, dated 06 August 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian _____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent _____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness _____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**STUDY INFORMATION LETTER**

**FOR SUBJECT'S PARENTS/GUARDIANS WHO SIGNED THE MODEL ICF VERSION 01 DATED: 06-AUG-2010**

**(For all the subjects in this study: Subjects in Efficacy subgroup, Immunogenicity subgroup 1 and Immunogenicity subgroup 2)**

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Information Letter version 1 dated 13 October 2010 (update with Version and date of Local information letter)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## Purpose of this document

By means of this document we want to thank you for your child's/ward's participation in this study. Through this information letter we want to inform you about the few updates which were made to the Rota-075 Informed Consent Form Version 01 dated 06 August 2010, a copy of which was handed over to you during the consent process. **Please take time to read the following information and ask us if you have any questions.** The following updates were done to the section titled "**What side effects or risks can you expect for your child/ward in the study?**"

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However, preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*, with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

Material from Porcine circovirus type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

Informed Consent Form for Efficacy subgroup

CONFIDENTIAL
113808 (ROTA-075)

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 02 (update with Version of Local ICF)**

**Date: 02 September 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease) and safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools

are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 2350 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she

is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit. |

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| Day | What will happen at this visit |
|---|---|
| | Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.
- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that**

**any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*, with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the

non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

Material from *Porcine circovirus* type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this

study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Efficacy subgroup Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 02, 15 pages, dated 02 September 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Efficacy subgroup Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian _____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent _____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness _____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 02 (update with Version of Local ICF)**

**Date: 02 September 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 600 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

Informed Consent Form- for Immunogenicity subgroup 1

**CONFIDENTIAL**

113808 (ROTA-075)

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 1

**CONFIDENTIAL**
113808 (ROTA-075)

**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 3 millilitres)<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination. |

| **Day** | **What will happen at this visit** |
|---|---|
| | Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit.<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination.<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the

next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*,

with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

Material from Porcine Circovirus type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from**

**samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

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## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 02, 15 pages, dated 02 September 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

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I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 02 (update with Version of Local ICF)**

**Date: 02 September 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 300 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she did not receive any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.
- He/she does not or has not had any history of diphtheria, tetanus and pertussis disease.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she does not have a disease that affects his/her nervous system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (Visit 6 = concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 2

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 4.5 millilitres)<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after Dose 1 of OPV vaccine<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>DTPa vaccine given on left thigh<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days |

| Day | What will happen at this visit |
|---|---|
| | (Days 0 – 7) after Dose 2 of OPV vaccine and Dose 1 of DTPa<br><br>Daily post-vaccination recording of solicited local adverse events within 8-days (Days 0 – 7) after Dose 1 of DTPa vaccine<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>Collection of blood sample (not more than 3 millilitres)<br><br>OPV vaccine given orally<br><br>DTPa vaccine given on left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br><br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 3 (Visit 4) | Return gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>DTPa vaccine injected on the left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and Visit 4)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 3 and Visit 4<br><br>Recording of any medical condition your child/ward has experienced between Visit 3 and Visit 4<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 4 (Visit 5) | Return gastroenteritis dairy cards given at previous visit |

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| Day | What will happen at this visit |
|---|---|
| | Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 4 and Visit 5)<br>Recording of any medication/vaccination your child/ward has received between Visit 4 and Visit 5<br>Recording of any medical condition your child/ward has experienced between Visit 4 and Visit 5<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age (Visit 6) | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 5 till your child/ward is one year of age [Visit 6])<br>Recording of any medication/vaccination your child/ward has received between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of any medical condition your child/ward has experienced between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of serious adverse events<br>Study Conclusion |

- DTPa vaccine is a vaccine against diphtheria, tetanus and pertussis [whooping cough]) and OPV vaccine is a vaccine against polio.

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.

- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.

  – body (axillary) temperature.

  – solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- You will receive diary cards to record information of your child/ward on the following after the first two doses of the OPV vaccine and the first dose of the DTPa vaccine

  – body (axillary) temperature.

  - solicited (expected) general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) for DTPa and OPV vaccine and solicited (expected) local symptoms (pain, swelling, redness) for DTPa vaccine occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

- Your child/ward will also receive his/her routine childhood vaccinations recommended in China.

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants

showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*, with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

Material from Porcine Circovirus type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

The following side effects may occur when your child/ward receives DTPa and OPV vaccines:

Like all medicines, DTPa can cause side effects, although not everybody gets them. Side effects that may occur are the following:

The following side effects related to study procedures may occur: (this may occur with up to more than 1 in 10 doses): irritability, sleepiness, redness and swelling at the injection site, fever (≥ 38.0°C).

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses): loss of appetite, restlessness, abnormal crying, diarrhoea, vomiting, itching, pain at the injection site.

The following side effects are less likely: (these may occur with up to 1 in 100 doses): headache, cough, bronchitis, rash, hard lump at the injection site, fatigue, fever (≥39.1°C)

The following side effects are rare: (these may occur 1 in 1000 doses of the vaccine): hives

The following side effects are very rare: (these may occur 1 in 10,000 doses of the vaccine):

As with all injectable vaccines, there is an extremely small risk of severe allergic reactions. These can be recognised by:

- Itchy rash of the hands and feet
- Swelling of the eyes and face
- Difficulty in breathing or swallowing.

These reactions will usually occur before leaving the doctor's surgery. However, if your child/ward gets any of these symptoms you should contact a doctor urgently.

- Swollen glands in the neck, armpit or groin
- Bleeding or bruising more easily than normal
- Collapse or periods of unconsciousness, lack of awareness, seizures or fits (with or without fever) which usually occur within 2 to 3 days after vaccination
- Temporarily stopping breathing
- Swelling of the entire injected limb

Like all medicines, OPV can cause side effects, although not everybody gets them. Side effects that may occur are the following:

Generally there are no adverse reactions after oral intake of OPV vaccine. The following side effects may occur in some subjects: fever, nausea, vomit, diarrhoea, and rashes. No special intervention is indicated generally, symptomatic treatment may be administered if necessary.

Vaccine associated paralytic poliomyelitis (VAPP) may be caused by inoculation of live attenuated poliomyelitis, and there is no exact statistical data domestically. VAPP incidence rates are 2-4 in one million, according to official statistical report by World Health Organization.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgments made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.

- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 02, 17 pages, dated 02 September 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

<*Note: Not applicable if study doctor is healthcare doctor.*>

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian _____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent _____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness _____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

Informed Consent Form Addendum

CONFIDENTIAL

Study Identification 113808 (ROTA-075)

**ADDENDUM 01 to the Informed Consent Form for the Subjects' Parents/ Legally Acceptable Representatives (LARs)**

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Version and date: Version 1–05 August 2011**

**Company Name: GlaxoSmithKline Biologicals S.A.**

**Subject Identification: _____**

*This document should be presented to the subject's LAR in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the subject's LAR.*

## Purpose of this document

This document is an addendum to the Informed Consent Form that you had signed at the start of the 113808 (ROTA-075) study.

As explained to you in the original informed consent form, the purpose of this study is to evaluate the efficacy, immune response and safety of GSK Biologicals' of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

The original ICF asked you if you would allow your child/ward to be part of this study till he/she is one year of age. However, during the study period lower number of rotavirus gastroenteritis cases were observed than anticipated. Therefore, in order to meet the primary objective of this study, the study participants are to be followed up till April 2012. If you agree to allow your child/ward to participate in this study extension, you will be asked to come to the study site for an additional visit (Visit 7).

Your consent is voluntary. Refusal will involve no penalty or loss of benefits or attention that your child is otherwise entitled to receive from your healthcare provider.

You should not sign this addendum unless you have received satisfactory answers to all of your questions. You will receive a signed copy of this addendum for your records.

Please find below the updated section entitled under the section "What does this study involve?" New text is shown in ***bold italics*** below:

The expected duration of your child's/ward's participation in this study ***will not exceed a maximum of 21 months*** (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

Informed Consent Form Addendum

**CONFIDENTIAL**

Study Identification 113808 (ROTA-075)

| | |
|---|---|
| ***Visit 6*** | ***Addendum to be signed by the child/ward's parents or guardians*** |
| ***After visit 6 for subjects who have already completed Visit 6*** | ***Addendum to be signed by the child/ward's parents or guardians***<br>***Retrospective recording of intercurrent medical condition***<br>***Retrospective recording concomitant medication/vaccination***<br>***Retrospective follow-up on GE episodes***<br>***Retrospective recording of SAEs*** |
| ***Visit 7 (April 2012)***<br><br>***(For all subjects participating in the extended follow-up period)*** | ***Addendum to be signed by the child/ward's parents or guardians***<br>***Return completed gastroenteritis dairy cards given at previous visit***<br>***Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 6 and Visit 7)***<br>***Recording of any medication/vaccination your child/ward has received between Visit 6 till Visit 7***<br>***Recording of any medical condition your child/ward has experienced between Visit 6 till Visit 7***<br>***Recording of serious adverse events***<br>***Study Conclusion*** |

Informed Consent Form Addendum Subject ID: _____

**CONFIDENTIAL**
Study Identification 113808 (ROTA-075)

## Consent statement

I,

_____
(Printed name of subject's parent/guardian)

the parent/ guardian of _____
Subject's name

- confirm that I have read the written information (or have had the information read to me) in the Addendum 01 Version 1-05 August 2011 to the Model ICF Version 1-06 August 2010 or Model ICF Version 2- 02 September 2010 (you may have received either one of the versions), for study 113808 (ROTA-075) and the changes have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my son /daughter to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my son /daughter to continue participating in the study.

I hereby agree to let my child continue to participate in this study.

| | | | |
|---|---|---|---|
| Printed name of subject's parent/guardian | _____ | Date: | |
| Signature of subject's parent/guardian | _____ | Date: | _____ day/ month/ year |
| Printed name of Witness (If needed) | _____ | | |
| *Signature of Witness | _____ | Date: | _____ day/ month/ year |
| Printed Name of Person explaining the *addendum* | _____ | | |
| Signature of Person explaining the *addendum* | _____ | Date: | _____ day/ month/ year |

*** Signature of witness is only required for those subject's whose parents/guardians are unable to sign their own name.**

# List of investigators and other important participants in the study, contact information and number and distribution of subjects

| Investigator's name | Sub-investigators | Centre number* | Investigational site | Location | Phone number<br>Fax number | Number of Subjects | % of Subjects |
|---|---|---|---|---|---|---|---|
| Dr. [redacted] | [redacted] | [redacted] | [redacted] | [redacted] China | Phone: [redacted]<br>Fax: [redacted]<br>E-mail: [redacted] | 923 | 27.6% |
| Dr. [redacted] | [redacted] | [redacted] | [redacted] | [redacted] China | Phone: [redacted]<br>Fax: [redacted]<br>E-mail: [redacted] | 904 | 27.0% |

| Investigator's name | Sub-investigators | Centre number* | Investigational site | Location | Phone number<br>Fax number | Number of Subjects | % of Subjects |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Dr. | | | | China | Phone:<br>Fax:<br>E-mail: | 1,201 | 35.9% |

| Investigator's name | Sub-investigators | Centre number* | Investigational site | Location | Phone number Fax number | Number of Subjects | % of Subjects |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Dr. | | | | China | Phone:<br>Fax:<br>E-mail: | 312 | 9.3% |

* GSK Biologicals' assigned centre number

# Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

*This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.*

# Signature of principal or coordinating investigator

## GlaxoSmithKline Biologicals
## Global Clinical Research and Development
## Investigator Approval Page

Please note that by signing this page, you take responsibility for the content of the Final Study Report, including appendices

STUDY TITLE: Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants

Study: 113808 (ROTA-075) 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: [redacted]

Affiliation /investigational centre: [redacted]

Signature of Investigator: _____

Date: _____

For internal use only

- ----------Checksum----------!Ver.!Created On - -
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# GlaxoSmithKline Biologicals
# Global Clinical Research and Development
# Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Final Study Report, including appendices

STUDY TITLE: Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants

Study: 113808 (ROTA-075) Development Phase: III

*I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Clinical Development,

Combination Vaccines (Infanrix/Boostrix/Hepatitis) and Rotavirus Vaccines, Global Vaccine Development

GlaxoSmithKline Biologicals

Signature: _____

Date: _____

For internal use only

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## Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable.

# Randomisation list

## Randomization List

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 1 | | [redacted] | 21 | | [redacted] | 41 | | [redacted] | 61 | | [redacted] | 81 | | [redacted] | 101 | | [redacted] | 121 | |
| | 1 | | | 21 | | | 41 | | | 61 | | | 81 | | | 101 | | | 121 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
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| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 141 | 141 | |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 161 | 161 | |
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| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. Bl. No nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 711 | |
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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. Bl. No nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] 991 | | [redacted] 1011 | | [redacted] 1031 | | [redacted] 454 | Y | [redacted] 474 | Y | [redacted] 494 | Y | [redacted] 514 | Y |
| 991 | | 1011 | | 1031 | | 454 | Y | 474 | Y | 494 | Y | 514 | Y |
| 992 | | 1012 | | 1032 | | 455 | Y | 475 | Y | 495 | Y | 515 | Y |
| 992 | | 1012 | | 1032 | | 455 | Y | 475 | Y | 495 | Y | 515 | Y |
| 993 | | 1013 | | 1033 | | 456 | Y | 476 | Y | 496 | Y | 516 | Y |
| 993 | | 1013 | | 1033 | | 456 | Y | 476 | Y | 496 | Y | 516 | Y |
| 994 | | 1014 | | 1034 | | 457 | Y | 477 | Y | 497 | Y | 517 | Y |
| 994 | | 1014 | | 1034 | | 457 | Y | 477 | Y | 497 | Y | 517 | Y |
| 995 | | 1015 | | 1035 | | 458 | Y | 478 | Y | 498 | Y | 518 | Y |
| 995 | | 1015 | | 1035 | | 458 | Y | 478 | Y | 498 | Y | 518 | Y |
| 996 | | 1016 | | 1036 | | 459 | Y | 479 | Y | 499 | Y | 519 | Y |
| 996 | | 1016 | | 1036 | | 459 | Y | 479 | Y | 499 | Y | 519 | Y |
| 997 | | 1017 | | 1037 | | 460 | Y | 480 | Y | 500 | Y | 520 | Y |
| 997 | | 1017 | | 1037 | | 460 | Y | 480 | Y | 500 | Y | 520 | Y |
| 998 | | 1018 | | 1038 | | 461 | Y | 481 | Y | 501 | Y | 521 | Y |
| 998 | | 1018 | | 1038 | | 461 | Y | 481 | Y | 501 | Y | 521 | Y |
| 999 | | 1019 | | 1039 | | 462 | Y | 482 | Y | 502 | Y | 522 | Y |
| 999 | | 1019 | | 1039 | | 462 | Y | 482 | Y | 502 | Y | 522 | Y |
| 1000 | | 1020 | | 1040 | | 463 | Y | 483 | Y | 503 | Y | 523 | Y |
| 1000 | | 1020 | | 1040 | | 463 | Y | 483 | Y | 503 | Y | 523 | Y |
| 1001 | | 1021 | | 1041 | | 464 | Y | 484 | Y | 504 | Y | 524 | Y |
| 1001 | | 1021 | | 1041 | | 464 | Y | 484 | Y | 504 | Y | 524 | Y |
| 1002 | | 1022 | | 1042 | | 465 | Y | 485 | Y | 505 | Y | 525 | Y |
| 1002 | | 1022 | | 1042 | | 465 | Y | 485 | Y | 505 | Y | 525 | Y |
| 1003 | | 1023 | | 1043 | | 466 | Y | 486 | Y | 506 | Y | 526 | Y |
| 1003 | | 1023 | | 1043 | | 466 | Y | 486 | Y | 506 | Y | 526 | Y |
| 1004 | | 1024 | | 1044 | | 467 | Y | 487 | Y | 507 | Y | 527 | Y |
| 1004 | | 1024 | | 1044 | | 467 | Y | 487 | Y | 507 | Y | 527 | Y |
| 1005 | | 1025 | | 448 | Y | 468 | Y | 488 | Y | 508 | Y | 528 | Y |
| 1005 | | 1025 | | 448 | Y | 468 | Y | 488 | Y | 508 | Y | 528 | Y |
| 1006 | | 1026 | | 449 | Y | 469 | Y | 489 | Y | 509 | Y | 529 | Y |
| 1006 | | 1026 | | 449 | Y | 469 | Y | 489 | Y | 509 | Y | 529 | Y |
| 1007 | | 1027 | | 450 | Y | 470 | Y | 490 | Y | 510 | Y | 530 | Y |
| 1007 | | 1027 | | 450 | Y | 470 | Y | 490 | Y | 510 | Y | 530 | Y |
| 1008 | | 1028 | | 451 | Y | 471 | Y | 491 | Y | 511 | Y | 531 | Y |
| 1008 | | 1028 | | 451 | Y | 471 | Y | 491 | Y | 511 | Y | 531 | Y |
| 1009 | | 1029 | | 452 | Y | 472 | Y | 492 | Y | 512 | Y | 532 | Y |
| 1009 | | 1029 | | 452 | Y | 472 | Y | 492 | Y | 512 | Y | 532 | Y |
| 1010 | | 1030 | | 453 | Y | 473 | Y | 493 | Y | 513 | Y | 533 | Y |
| 1010 | | 1030 | | 453 | Y | 473 | Y | 493 | Y | 513 | Y | 533 | Y |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 1081 | | Y |
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| | 1100 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 1101 | | Y |
| | 1101 | | Y |
| | 1102 | | Y |
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| | 1119 | | Y |
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| | 1120 | | Y |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 1121 | Y | [redacted] | 1141 | Y | [redacted] | 1161 | Y | [redacted] | 1181 | Y |
| | 1121 | Y | | 1141 | Y | | 1161 | Y | | 1181 | Y |
| | 1122 | Y | | 1142 | Y | | 1162 | Y | | 1182 | Y |
| | 1122 | Y | | 1142 | Y | | 1162 | Y | | 1182 | Y |
| | 1123 | Y | | 1143 | Y | | 1163 | Y | | 1183 | Y |
| | 1123 | Y | | 1143 | Y | | 1163 | Y | | 1183 | Y |
| | 1124 | Y | | 1144 | Y | | 1164 | Y | | 1184 | Y |
| | 1124 | Y | | 1144 | Y | | 1164 | Y | | 1184 | Y |
| | 1125 | Y | | 1145 | Y | | 1165 | Y | | 1185 | Y |
| | 1125 | Y | | 1145 | Y | | 1165 | Y | | 1185 | Y |
| | 1126 | Y | | 1146 | Y | | 1166 | Y | | 1186 | Y |
| | 1126 | Y | | 1146 | Y | | 1166 | Y | | 1186 | Y |
| | 1127 | Y | | 1147 | Y | | 1167 | Y | | 1187 | Y |
| | 1127 | Y | | 1147 | Y | | 1167 | Y | | 1187 | Y |
| | 1128 | Y | | 1148 | Y | | 1168 | Y | | 1188 | Y |
| | 1128 | Y | | 1148 | Y | | 1168 | Y | | 1188 | Y |
| | 1129 | Y | | 1149 | Y | | 1169 | Y | | 1189 | Y |
| | 1129 | Y | | 1149 | Y | | 1169 | Y | | 1189 | Y |
| | 1130 | Y | | 1150 | Y | | 1170 | Y | | 1190 | Y |
| | 1130 | Y | | 1150 | Y | | 1170 | Y | | 1190 | Y |
| | 1131 | Y | | 1151 | Y | | 1171 | Y | | 1191 | Y |
| | 1131 | Y | | 1151 | Y | | 1171 | Y | | 1191 | Y |
| | 1132 | Y | | 1152 | Y | | 1172 | Y | | 1192 | Y |
| | 1132 | Y | | 1152 | Y | | 1172 | Y | | 1192 | Y |
| | 1133 | Y | | 1153 | Y | | 1173 | Y | | 1193 | Y |
| | 1133 | Y | | 1153 | Y | | 1173 | Y | | 1193 | Y |
| | 1134 | Y | | 1154 | Y | | 1174 | Y | | 1194 | Y |
| | 1134 | Y | | 1154 | Y | | 1174 | Y | | 1194 | Y |
| | 1135 | Y | | 1155 | Y | | 1175 | Y | | | |
| | 1135 | Y | | 1155 | Y | | 1175 | Y | | | |
| | 1136 | Y | | 1156 | Y | | 1176 | Y | | | |
| | 1136 | Y | | 1156 | Y | | 1176 | Y | | | |
| | 1137 | Y | | 1157 | Y | | 1177 | Y | | | |
| | 1137 | Y | | 1157 | Y | | 1177 | Y | | | |
| | 1138 | Y | | 1158 | Y | | 1178 | Y | | | |
| | 1138 | Y | | 1158 | Y | | 1178 | Y | | | |
| | 1139 | Y | | 1159 | Y | | 1179 | Y | | | |
| | 1139 | Y | | 1159 | Y | | 1179 | Y | | | |
| | 1140 | Y | | 1160 | Y | | 1180 | Y | | | |
| | 1140 | Y | | 1160 | Y | | 1180 | Y | | | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 1 | | [redacted] | 21 | | [redacted] | 41 | | [redacted] | 61 | | [redacted] | 81 | | [redacted] | 101 | | [redacted] | 121 | |
| | 1 | | | 21 | | | 41 | | | 61 | | | 81 | | | 101 | | | 121 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |
| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag |
|---|---|
| [redacted] | 141 |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 161 |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 421 | [redacted] | 441 | [redacted] | 611 | [redacted] | 631 | [redacted] | 651 | [redacted] | 671 | [redacted] | 691 |
| | 421 | | 441 | | 611 | | 631 | | 651 | | 671 | | 691 |
| | 422 | | 442 | | 612 | | 632 | | 652 | | 672 | | 692 |
| | 422 | | 442 | | 612 | | 632 | | 652 | | 672 | | 692 |
| | 423 | | 443 | | 613 | | 633 | | 653 | | 673 | | 693 |
| | 423 | | 443 | | 613 | | 633 | | 653 | | 673 | | 693 |
| | 424 | | 444 | | 614 | | 634 | | 654 | | 674 | | 694 |
| | 424 | | 444 | | 614 | | 634 | | 654 | | 674 | | 694 |
| | 425 | | 445 | | 615 | | 635 | | 655 | | 675 | | 695 |
| | 425 | | 445 | | 615 | | 635 | | 655 | | 675 | | 695 |
| | 426 | | 446 | | 616 | | 636 | | 656 | | 676 | | 696 |
| | 426 | | 446 | | 616 | | 636 | | 656 | | 676 | | 696 |
| | 427 | | 447 | | 617 | | 637 | | 657 | | 677 | | 697 |
| | 427 | | 447 | | 617 | | 637 | | 657 | | 677 | | 697 |
| | 428 | | 598 | | 618 | | 638 | | 658 | | 678 | | 698 |
| | 428 | | 598 | | 618 | | 638 | | 658 | | 678 | | 698 |
| | 429 | | 599 | | 619 | | 639 | | 659 | | 679 | | 699 |
| | 429 | | 599 | | 619 | | 639 | | 659 | | 679 | | 699 |
| | 430 | | 600 | | 620 | | 640 | | 660 | | 680 | | 700 |
| | 430 | | 600 | | 620 | | 640 | | 660 | | 680 | | 700 |
| | 431 | | 601 | | 621 | | 641 | | 661 | | 681 | | 701 |
| | 431 | | 601 | | 621 | | 641 | | 661 | | 681 | | 701 |
| | 432 | | 602 | | 622 | | 642 | | 662 | | 682 | | 702 |
| | 432 | | 602 | | 622 | | 642 | | 662 | | 682 | | 702 |
| | 433 | | 603 | | 623 | | 643 | | 663 | | 683 | | 703 |
| | 433 | | 603 | | 623 | | 643 | | 663 | | 683 | | 703 |
| | 434 | | 604 | | 624 | | 644 | | 664 | | 684 | | 704 |
| | 434 | | 604 | | 624 | | 644 | | 664 | | 684 | | 704 |
| | 435 | | 605 | | 625 | | 645 | | 665 | | 685 | | 705 |
| | 435 | | 605 | | 625 | | 645 | | 665 | | 685 | | 705 |
| | 436 | | 606 | | 626 | | 646 | | 666 | | 686 | | 706 |
| | 436 | | 606 | | 626 | | 646 | | 666 | | 686 | | 706 |
| | 437 | | 607 | | 627 | | 647 | | 667 | | 687 | | 707 |
| | 437 | | 607 | | 627 | | 647 | | 667 | | 687 | | 707 |
| | 438 | | 608 | | 628 | | 648 | | 668 | | 688 | | 708 |
| | 438 | | 608 | | 628 | | 648 | | 668 | | 688 | | 708 |
| | 439 | | 609 | | 629 | | 649 | | 669 | | 689 | | 709 |
| | 439 | | 609 | | 629 | | 649 | | 669 | | 689 | | 709 |
| | 440 | | 610 | | 630 | | 650 | | 670 | | 690 | | 710 |
| | 440 | | 610 | | 630 | | 650 | | 670 | | 690 | | 710 |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 711 | [redacted] | 731 | [redacted] | 751 | [redacted] | 771 | [redacted] | 791 | [redacted] | 811 | [redacted] | 831 |
| | 711 | | 731 | | 751 | | 771 | | 791 | | 811 | | 831 |
| | 712 | | 732 | | 752 | | 772 | | 792 | | 812 | | 832 |
| | 712 | | 732 | | 752 | | 772 | | 792 | | 812 | | 832 |
| | 713 | | 733 | | 753 | | 773 | | 793 | | 813 | | 833 |
| | 713 | | 733 | | 753 | | 773 | | 793 | | 813 | | 833 |
| | 714 | | 734 | | 754 | | 774 | | 794 | | 814 | | 834 |
| | 714 | | 734 | | 754 | | 774 | | 794 | | 814 | | 834 |
| | 715 | | 735 | | 755 | | 775 | | 795 | | 815 | | 835 |
| | 715 | | 735 | | 755 | | 775 | | 795 | | 815 | | 835 |
| | 716 | | 736 | | 756 | | 776 | | 796 | | 816 | | 836 |
| | 716 | | 736 | | 756 | | 776 | | 796 | | 816 | | 836 |
| | 717 | | 737 | | 757 | | 777 | | 797 | | 817 | | 837 |
| | 717 | | 737 | | 757 | | 777 | | 797 | | 817 | | 837 |
| | 718 | | 738 | | 758 | | 778 | | 798 | | 818 | | 838 |
| | 718 | | 738 | | 758 | | 778 | | 798 | | 818 | | 838 |
| | 719 | | 739 | | 759 | | 779 | | 799 | | 819 | | 839 |
| | 719 | | 739 | | 759 | | 779 | | 799 | | 819 | | 839 |
| | 720 | | 740 | | 760 | | 780 | | 800 | | 820 | | 840 |
| | 720 | | 740 | | 760 | | 780 | | 800 | | 820 | | 840 |
| | 721 | | 741 | | 761 | | 781 | | 801 | | 821 | | 841 |
| | 721 | | 741 | | 761 | | 781 | | 801 | | 821 | | 841 |
| | 722 | | 742 | | 762 | | 782 | | 802 | | 822 | | 842 |
| | 722 | | 742 | | 762 | | 782 | | 802 | | 822 | | 842 |
| | 723 | | 743 | | 763 | | 783 | | 803 | | 823 | | 843 |
| | 723 | | 743 | | 763 | | 783 | | 803 | | 823 | | 843 |
| | 724 | | 744 | | 764 | | 784 | | 804 | | 824 | | 844 |
| | 724 | | 744 | | 764 | | 784 | | 804 | | 824 | | 844 |
| | 725 | | 745 | | 765 | | 785 | | 805 | | 825 | | 845 |
| | 725 | | 745 | | 765 | | 785 | | 805 | | 825 | | 845 |
| | 726 | | 746 | | 766 | | 786 | | 806 | | 826 | | 846 |
| | 726 | | 746 | | 766 | | 786 | | 806 | | 826 | | 846 |
| | 727 | | 747 | | 767 | | 787 | | 807 | | 827 | | 847 |
| | 727 | | 747 | | 767 | | 787 | | 807 | | 827 | | 847 |
| | 728 | | 748 | | 768 | | 788 | | 808 | | 828 | | 848 |
| | 728 | | 748 | | 768 | | 788 | | 808 | | 828 | | 848 |
| | 729 | | 749 | | 769 | | 789 | | 809 | | 829 | | 849 |
| | 729 | | 749 | | 769 | | 789 | | 809 | | 829 | | 849 |
| | 730 | | 750 | | 770 | | 790 | | 810 | | 830 | | 850 |
| | 730 | | 750 | | 770 | | 790 | | 810 | | 830 | | 850 |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 871 |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 891 |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 911 |
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| Trt. Bl. No nb | Repl. flag |
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SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] 991 | | [redacted] 1011 | | [redacted] 1031 | | [redacted] 454 | Y | [redacted] 474 | Y | [redacted] 494 | Y | [redacted] 514 | Y |
| 991 | | 1011 | | 1031 | | 454 | Y | 474 | Y | 494 | Y | 514 | Y |
| 992 | | 1012 | | 1032 | | 455 | Y | 475 | Y | 495 | Y | 515 | Y |
| 992 | | 1012 | | 1032 | | 455 | Y | 475 | Y | 495 | Y | 515 | Y |
| 993 | | 1013 | | 1033 | | 456 | Y | 476 | Y | 496 | Y | 516 | Y |
| 993 | | 1013 | | 1033 | | 456 | Y | 476 | Y | 496 | Y | 516 | Y |
| 994 | | 1014 | | 1034 | | 457 | Y | 477 | Y | 497 | Y | 517 | Y |
| 994 | | 1014 | | 1034 | | 457 | Y | 477 | Y | 497 | Y | 517 | Y |
| 995 | | 1015 | | 1035 | | 458 | Y | 478 | Y | 498 | Y | 518 | Y |
| 995 | | 1015 | | 1035 | | 458 | Y | 478 | Y | 498 | Y | 518 | Y |
| 996 | | 1016 | | 1036 | | 459 | Y | 479 | Y | 499 | Y | 519 | Y |
| 996 | | 1016 | | 1036 | | 459 | Y | 479 | Y | 499 | Y | 519 | Y |
| 997 | | 1017 | | 1037 | | 460 | Y | 480 | Y | 500 | Y | 520 | Y |
| 997 | | 1017 | | 1037 | | 460 | Y | 480 | Y | 500 | Y | 520 | Y |
| 998 | | 1018 | | 1038 | | 461 | Y | 481 | Y | 501 | Y | 521 | Y |
| 998 | | 1018 | | 1038 | | 461 | Y | 481 | Y | 501 | Y | 521 | Y |
| 999 | | 1019 | | 1039 | | 462 | Y | 482 | Y | 502 | Y | 522 | Y |
| 999 | | 1019 | | 1039 | | 462 | Y | 482 | Y | 502 | Y | 522 | Y |
| 1000 | | 1020 | | 1040 | | 463 | Y | 483 | Y | 503 | Y | 523 | Y |
| 1000 | | 1020 | | 1040 | | 463 | Y | 483 | Y | 503 | Y | 523 | Y |
| 1001 | | 1021 | | 1041 | | 464 | Y | 484 | Y | 504 | Y | 524 | Y |
| 1001 | | 1021 | | 1041 | | 464 | Y | 484 | Y | 504 | Y | 524 | Y |
| 1002 | | 1022 | | 1042 | | 465 | Y | 485 | Y | 505 | Y | 525 | Y |
| 1002 | | 1022 | | 1042 | | 465 | Y | 485 | Y | 505 | Y | 525 | Y |
| 1003 | | 1023 | | 1043 | | 466 | Y | 486 | Y | 506 | Y | 526 | Y |
| 1003 | | 1023 | | 1043 | | 466 | Y | 486 | Y | 506 | Y | 526 | Y |
| 1004 | | 1024 | | 1044 | | 467 | Y | 487 | Y | 507 | Y | 527 | Y |
| 1004 | | 1024 | | 1044 | | 467 | Y | 487 | Y | 507 | Y | 527 | Y |
| 1005 | | 1025 | | 448 | Y | 468 | Y | 488 | Y | 508 | Y | 528 | Y |
| 1005 | | 1025 | | 448 | Y | 468 | Y | 488 | Y | 508 | Y | 528 | Y |
| 1006 | | 1026 | | 449 | Y | 469 | Y | 489 | Y | 509 | Y | 529 | Y |
| 1006 | | 1026 | | 449 | Y | 469 | Y | 489 | Y | 509 | Y | 529 | Y |
| 1007 | | 1027 | | 450 | Y | 470 | Y | 490 | Y | 510 | Y | 530 | Y |
| 1007 | | 1027 | | 450 | Y | 470 | Y | 490 | Y | 510 | Y | 530 | Y |
| 1008 | | 1028 | | 451 | Y | 471 | Y | 491 | Y | 511 | Y | 531 | Y |
| 1008 | | 1028 | | 451 | Y | 471 | Y | 491 | Y | 511 | Y | 531 | Y |
| 1009 | | 1029 | | 452 | Y | 472 | Y | 492 | Y | 512 | Y | 532 | Y |
| 1009 | | 1029 | | 452 | Y | 472 | Y | 492 | Y | 512 | Y | 532 | Y |
| 1010 | | 1030 | | 453 | Y | 473 | Y | 493 | Y | 513 | Y | 533 | Y |
| 1010 | | 1030 | | 453 | Y | 473 | Y | 493 | Y | 513 | Y | 533 | Y |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 534 | | Y |
| | 534 | | Y |
| | 535 | | Y |
| | 535 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 554 | | Y |
| | 554 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 574 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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| | 1110 | | Y |
| | 1110 | | Y |
| | 1111 | | Y |
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| | 1119 | | Y |
| | 1119 | | Y |
| | 1120 | | Y |
| | 1120 | | Y |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|
| [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| 1121 | Y | 1141 | Y | 1161 | Y | 1181 | Y |
| 1121 | Y | 1141 | Y | 1161 | Y | 1181 | Y |
| 1122 | Y | 1142 | Y | 1162 | Y | 1182 | Y |
| 1122 | Y | 1142 | Y | 1162 | Y | 1182 | Y |
| 1123 | Y | 1143 | Y | 1163 | Y | 1183 | Y |
| 1123 | Y | 1143 | Y | 1163 | Y | 1183 | Y |
| 1124 | Y | 1144 | Y | 1164 | Y | 1184 | Y |
| 1124 | Y | 1144 | Y | 1164 | Y | 1184 | Y |
| 1125 | Y | 1145 | Y | 1165 | Y | 1185 | Y |
| 1125 | Y | 1145 | Y | 1165 | Y | 1185 | Y |
| 1126 | Y | 1146 | Y | 1166 | Y | 1186 | Y |
| 1126 | Y | 1146 | Y | 1166 | Y | 1186 | Y |
| 1127 | Y | 1147 | Y | 1167 | Y | 1187 | Y |
| 1127 | Y | 1147 | Y | 1167 | Y | 1187 | Y |
| 1128 | Y | 1148 | Y | 1168 | Y | 1188 | Y |
| 1128 | Y | 1148 | Y | 1168 | Y | 1188 | Y |
| 1129 | Y | 1149 | Y | 1169 | Y | 1189 | Y |
| 1129 | Y | 1149 | Y | 1169 | Y | 1189 | Y |
| 1130 | Y | 1150 | Y | 1170 | Y | 1190 | Y |
| 1130 | Y | 1150 | Y | 1170 | Y | 1190 | Y |
| 1131 | Y | 1151 | Y | 1171 | Y | 1191 | Y |
| 1131 | Y | 1151 | Y | 1171 | Y | 1191 | Y |
| 1132 | Y | 1152 | Y | 1172 | Y | 1192 | Y |
| 1132 | Y | 1152 | Y | 1172 | Y | 1192 | Y |
| 1133 | Y | 1153 | Y | 1173 | Y | 1193 | Y |
| 1133 | Y | 1153 | Y | 1173 | Y | 1193 | Y |
| 1134 | Y | 1154 | Y | 1174 | Y | 1194 | Y |
| 1134 | Y | 1154 | Y | 1174 | Y | 1194 | Y |
| 1135 | Y | 1155 | Y | 1175 | Y | | |
| 1135 | Y | 1155 | Y | 1175 | Y | | |
| 1136 | Y | 1156 | Y | 1176 | Y | | |
| 1136 | Y | 1156 | Y | 1176 | Y | | |
| 1137 | Y | 1157 | Y | 1177 | Y | | |
| 1137 | Y | 1157 | Y | 1177 | Y | | |
| 1138 | Y | 1158 | Y | 1178 | Y | | |
| 1138 | Y | 1158 | Y | 1178 | Y | | |
| 1139 | Y | 1159 | Y | 1179 | Y | | |
| 1139 | Y | 1159 | Y | 1179 | Y | | |
| 1140 | Y | 1160 | Y | 1180 | Y | | |
| 1140 | Y | 1160 | Y | 1180 | Y | | |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1195 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1235 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1275 | |
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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1355 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1395 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1435 | |
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Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1475 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1515 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1555 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1595 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1635 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 1675 | |
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| Trt. No | Bl. nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. Bl. No nb | Repl. flag |
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| [redacted] 1755 | |
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| Trt. Bl. No nb | Repl. flag |
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| Trt. Bl. No nb | Repl. flag |
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| Trt. Bl. No nb | Repl. flag |
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| 2033 | |
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Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. No | Bl. nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

OPV

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Randomisation list

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Randomisation list

ROTA-075 (A.31AUG2012)

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Randomisation list

ROTA-075 (A.31AUG2012)

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Randomisation list

ROTA-075 (A.31AUG2012)

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# Audit Certificates

# AUDIT CERTIFICATE

**Study Number: ROTA 075 (113808)**

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312).

During the conduct and reporting of this/these study(s), the following independent audits were performed by or on behalf of GlaxoSmithKline.

| Study Number | Type | Conducted by | Centre number | Country | Audit Date |
|---|---|---|---|---|---|
| 113808 | Investigator Site | GSK CDQA | [redacted] | China | 26-27 June, 2011 |

Clinical Development Quality Assurance hereby confirm that the audits detailed above were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

**Name:** [redacted] **Date:** 11 October, 2012

**Role:** Manager, CDQA

**Clinical Development Quality Assurance**
**GlaxoSmithKline Research and Development**

## Documentation of statistical methods

Refer to the Study Report.

## Documentation of inter-laboratory standardisation methods and quality assurance procedures

Not applicable.

## Publications based on the study

Not applicable.

*This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.*

# Individual Listings

# NOTES TO APPENDIX TABLES

***The following abbreviations are common throughout the Appendix tables:***

| | | | |
|---|---|---|---|
| Sub. No. | | : | Subject number |
| Eli MA | | : | Eligibility (MA: Main Analysis) |
| | E | : | Eliminated from reactogenicity and immunogenicity analyses |
| | I | : | Eliminated from immunogenicity analysis |
| | MC | : | Missing Confirmed |
| | N | : | No |
| | Y | : | Yes |
| | NA | : | Not Applicable |

***Abbreviations which are unique to a particular appendix are presented below.***

## Appendix Table IA - Individual subject data: Elimination codes

Elim Codes : Elimination codes

## Appendix Table I.B - Individual subject data: Demography

| | | | |
|---|---|---|---|
| Sex | | : | Sex |
| | F | : | Female |
| | M | : | Male |
| Centre | | : | Study centre |

## Appendix Table ICi - Individual subject data: Dates of Birth - vaccination - sampling - visits

Dates of vaccine administration,
Dates of sampling,
Dates of visits

| | | |
|---|---|---|
| VIS ND | : | Visit Not Done (the subject did not come) |
| VAC ND | : | Study vaccine administration not done |
| ND | : | Not Done |

## Appendix Table ICii - Individual subject data: Reason for visit not done

| | | | |
|---|---|---|---|
| Reason | | : | Reason for visit not done |
| | AEX | : | Non serious adverse event |
| | SAE | : | Serious adverse event |
| | OTH | : | Other |
| | SAM | : | Same reason and decision as previous visit |

## Appendix Table ID - Individual subject data: General medical history - Physical examination

Status

| | | |
|---|---|---|
| PAST | : | Medical history no more present at the physical examination |
| CURRENT | : | Medical history present at the physical examination |
| Both | : | Past and current |

## Appendix Table IE - Individual subject data: CONCLUSION

| | | | |
|---|---|---|---|
| Elim Crit | | : | Did any elimination criteria become applicable during the study? |
| | Y | : | Yes |
| | N | : | No |
| Link to AE | | : | Is the withdrawal of the subject linked to an adverse event ? |
| | Yes | : | |
| | No | : | |
| Date of last contact | | | Date when last information was collected on subject's condition |
| Good Condition? | | | Was the subject in good condition at date of last contact? |
| SAE? | | : | Did the subject experience any Serious Adverse Event during the |
| | | : | study? |
| | Y | : | Yes |
| | N | | No |
| Nb of SAE | | : | Total number of SAE's recorded in SAE report. |
| Preg | | : | Did the subject become pregnant during the study / since the end of the active phase? |

## Appendix Table IG - Individual subject data: Vaccination procedure for each subject: list of the administered vaccines and all related information

| | | | |
|---|---|---|---|
| Trt. No. | | : | Treatment number |
| According to Prot? | | : | Is of the study vaccine be administered according to protocol in terms of side/site/route? |
| Injection? | | : | Vaccine administration |
| Type of vacc. | | | |
| | 1 | : | Study vaccine not administered according to protocol: wrong side/site/route or replacement or wrong vial number |
| | 2 | : | Study vaccine planned but not administered for a given visit |
| | 3 | : | Administration of a study vaccine not planned in the group |
| Eff Vial Number | | : | Effective vial number administered |

## Appendix Table II - Individual subject data: Reason for vaccine not administered

| | | |
|---|---|---|
| Adm? | : | Study vaccine administration |
| N | : | Not administered |
| R | : | Replacement |
| S | : | Study vaccine |

| | | | |
|---|---|---|---|
| | W | : | Wrong vial number |
| Reason | | : | Reason why the study vaccine was not administered: |
| | SAE | : | Serious adverse event |
| | AEX | : | Non serious adverse event |
| | OTH | : | Other |

## Appendix Table IJ - Individual subject data: Reason for non-Eligibility

| | | | |
|---|---|---|---|
| Eligib. | | : | Did the subject meet all the entry criteria? |
| | No | : | Some inclusion /exclusion criteria are not met |
| Study vacc. | | | |
| | Yes | : | The subject received at least one dose of study vaccine (study vaccine, Replacement or Wrong vial number) |
| | No | : | No vaccine received |
| Criterion number | | : | Inclusion OR exclusion criteria number the subject failed |
| Reason of inclusion and exclusion criteria | | : | Description of the criterion number: label from codelist or 'Cfr. description in CRF' |

## Appendix Table IIA - Individual subject data: Solicited local adverse events

| | | | |
|---|---|---|---|
| L? | | : | Has the subject experienced any local symptoms? |
| | U | : | Information not available |
| | NA | : | Not Applicable (when the study vaccine was not administered) |
| | N | : | No |
| | Y | : | Yes |
| | M | : | Missing |
| VACC CODE | | : | Vaccine code (corresponding vaccine label presented on the first page of Appendix Table IIA) |
| VA | | : | Vaccine administration |
| | N | : | Not administered |
| | R | : | Replacement |
| | S | : | Study vaccine |
| | W | : | Wrong vial number |
| PA | | : | Pain (empty or scored from 0 to 3) |
| RE | | : | Redness (greatest diameter) |
| SW | | : | Swelling (greatest diameter) |
| IN | | : | Induration (greatest diameter) |
| EC | | : | Ecchymosis (greatest diameter) |
| EXP | | : | Has the subject experienced some symptoms? |
| | Y | : | Yes |
| | N | : | No |
| MA_TYPE | | : | Medical advice sought for the symptom |
| | ER | : | Emergency room |
| | HO | : | Hospitalization |
| | MD | : | Medical doctor |
| O? | | : | Ongoing at the end of the solicited follow-up period? |
| | Y | : | Yes |

| | | | |
|---|---|---|---|
| | N | : | No |
| Last day | | : | Date of the last day of symptom if it was ongoing after the solicited follow-up period |

## Appendix table IIB - Individual subject data: Solicited general adverse events

| | | | |
|---|---|---|---|
| G? | | : | Has the subject experienced any general symptoms? |
| | U | : | Information not available |
| | NA | : | Not Applicable (when the study vaccine was not administered) |
| | N | : | No |
| | Y | : | Yes |
| | M | : | Missing |
| AC | | : | General aches (empty or scored from 0 to 3) |
| AR | | : | Arthralgia (empty or scored from 0 to 3) |
| DA | | : | Diarrhoea (empty or scored from 0 to 3) |
| DR | | : | Drowsiness (empty or scored from 0 to 3) |
| FA | | : | Fatigue (empty or scored from 0 to 3) |
| FE | | : | Fever = Body temperature in °Cs or °Fs |
| FU | | : | Fussiness (empty or scored from 0 to 3) |
| GI | | : | Gastrointestinal symptoms (empty or scored from 0 to 3) |
| HE | | : | Headache (empty or scored from 0 to 3) |
| IR | | : | Irritability/fussiness (empty or scored from 0 to 3) |
| LO | | : | Loss of appetite (empty or scored from 0 to 3) |
| MA | | : | Malaise (empty or scored from 0 to 3) |
| MY | | : | Myalgia (empty or scored from 0 to 3) |
| NA | | : | Nausea (empty or scored from 0 to 3) |
| SL | | : | Sleeping less than usual (empty or scored from 0 to 3) |
| SH | | : | Shivering (empty or scored from 0 to 3) |
| SW | | : | Sweating (empty or scored from 0 to 3) |
| UC | | : | Unusual crying (empty or scored from 0 to 3) |
| VO | | : | Vomiting (empty or scored from 0 to 3) |
| TE | | : | Temperature = Body temperature in °Cs or °Fs |
| | RTE | : | Route (for body temperature recording) |
| | O | : | Oral |
| | A | : | Axillary |
| | R | : | Rectal |
| | T | : | Tympanic |
| | X | : | Tympanic oral |
| | Y | : | Tympanic rectal |
| | Rte Pre | : | Route for pre-vaccination temperature recording |
| | Pre Vac | : | Pre-vaccination temperature |
| EXP | | : | Symptom experienced |
| Caus | | : | Causality |
| MA TYPE | | : | Medical advice sought for the symptom |
| | ER | : | Emergency room |
| | HO | : | Hospitalization |
| | MD | : | Medical doctor |
| O? | | : | Ongoing at the end of the solicited follow-up period? |

| | | | |
|---|---|---|---|
| | Y | : | Yes |
| | N | : | No |
| Last day | | : | Date of the last day of symptom if it was ongoing after the solicited follow-up period |

## Appendix table IIC - Individual subject data: Unsolicited Adverse Event

| | | | |
|---|---|---|---|
| Verbatim | | : | Description of experience as recorded in the case report form |
| Keyword (MedDRA) | | : | Specific identification terminology linked to MedDRA classification codes |
| LLT MedDRA code | | : | Lower Level Term Code for MedDRA, Lowest level of the terminology, related to a single PT as a synonym, lexical variant, or quasi-synonym. (All PTs have an identical LLT). |
| Preferred term | | : | Medical term assigned to the keyword/verbatim, Represents a single medical concept |
| SOC code | | : | Primary System Organ Class code: Highest level of the terminology, and distinguished by anatomical or physiological system, etiology, or purpose |
| Chro | | : | Chronic illness |
| Pr Do | | : | Study vaccine dose given prior to the adverse event |
| M? | | : | Medical advice sought for the symptom |
| Type | | : | Type of medical advice |
| | ER | : | Emergency room |
| | HO | : | Hospitalization |
| | MD | : | Medical doctor |
| Caus | | : | Reasonable possibility that the AE have been caused by the investigational product? |
| Start date | | : | Date of onset of adverse event |
| Imm Pst Vac | | : | Adverse event starting during immediate post-vaccination period |
| Day onset | | : | Number of days since last study vaccine dose |
| End date | | : | Date of end of adverse event |
| Dur (d) | | : | Duration (days) of adverse event |
| Int | | : | Maximum intensity |
| | 1 | : | Mild |
| | 2 | : | Moderate |
| | 3 | : | Severe |
| L/G | | : | Local or general symptom |
| Out | | : | Outcome |
| | 1 | : | Recovered/Resolved |
| | 2 | : | Recovering/Resolving |
| | 3 | : | Not recovered/Not resolved |
| | 4 | : | Recovered with sequelae/Resolved with sequelae |
| | 5 | : | Died |
| Vacc Code | | : | Vaccine code (corresponding vaccine label presented on the first page of Appendix Tables IIC) |
| Ser | | : | Serious adverse event |

## Appendix tables IIDi - Individual subject data: Medication

| | | | |
|---|---|---|---|
| Prev dose | | : | Previous study vaccine dose |
| Rel. day of onset | | : | Day of onset of medication, relative to previous study vaccine dose |
| Start date | | : | Start date of medication |
| End date | | : | End date of medication |
| Dur (day) | | : | Duration (days) of medication |
| Trade-Generic name | | : | Trade and/or generic name of medication |
| Medical indication | | : | Medical indication for which medication was used |
| GSK Antibiot | | : | Antibiotic |
| | Y | : | Yes |
| GSK Antipyr | | : | Antipyretic |
| | Y | : | Yes |
| Proph | | : | Prophylactic medication |
| | Y | : | Yes |

## Appendix table IIDii - Individual subject data: Concomitant Vaccination

| | | |
|---|---|---|
| Trade name | : | Trade name of concomitant vaccine administered |
| Admin. date | : | Date of administration of concomitant vaccine |
| Previous vaccination date | : | Date of administration of previous study vaccine dose |
| Prev dose | : | Previous study vaccine dose |
| Rel. day of onset | : | Day of onset of concomitant vaccination, relative to date of previous study vaccine dose |

## Appendix table IVA - Gastroenteritis stool sample results

| | | |
|---|---|---|
| Visit | : | Related GE visit |
| Episode Number | : | Gastroenteritis episode Number |
| Collection date | : | Stool sample collection date |
| Collection date | : | Stool sample collection time |
| Onset day | : | Number of days since last study vaccine dose |
| Prev. vacc. dose | : | Previous study vaccine dose |
| Result | : | Stool Sample result |
| QNS | : | Quantity of sample not sufficient |
| POS | : | Positive |
| NEG | : | Negative |
| Master ID | : | Test Identifier |
| Variant ID | : | Test Identifier |
| Transfer ID | : | Test Identifier |

## Appendix table VA - Detailed information on Gastroenteritis episode

| | | |
|---|---|---|
| Episode Number | : | Gastroenteritis episode Number |
| Sample date | : | Stool sample collection date |
| Sample date | : | Stool sample collection time |
| Day of onset | : | Number of days since last study vaccine dose |

| | | |
|---|---|---|
| Vacc. dose | : | Previous study vaccine dose |
| Treatment | : | Treatment received Yes/No? |
| Treatment Type | : | Type of treatment |
| Treatment Specification | : | Type of treatment if type of treatment is “OTHER” |
| Medical Advice | : | Type of Medical Advice |
| Med. date | : | Medical advice date |
| No: of LTNS/ day | : | Number of Looser than normal stools per day |
| No: of Vomi. Epi./ day | : | Number of vomiting episodes per day |
| Sample Date | : | Sample collection date |
| Sample Time | : | Sample collection time |
| Temp. value in CE | : | Temperature Value in CE |

*This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*

# Statistical Analysis Plan Approval

| | |
|---|---|
| **Protocol Title:** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants |
| **eTrack study number** | 113808 |
| **eTrack abbreviated title** | Rota-075 |
| **Protocol version/date**<br><br>**Scope:** | Amendment 2: 05 August 2011<br><br>All data pertaining to the above study |
| **Version:**<br><br>**Date:** | Amendment 3<br><br>07-May-2013 |
| **Co-ordinating author:** | [redacted] |
| **Other author(s):** | [redacted] |

**Approved by:**

| | | | |
|---|---|---|---|
| **Lead Clinical Development, Combination Vaccines and Rotavirus Vaccines, Clinical Development Manager** | [redacted] | | |
| | Name | Signature | dd-mmm-yyyy |
| | | | |
| **Clinical Development Manager, Rotavirus vaccines** | [redacted] | | |
| | Name | Signature | dd-mmm-yyyy |
| | | | |
| **Project Statistician** | [redacted] | | |
| | Name | Signature | dd-mmm-yyyy |
| | | | |
| **Lead Statistician** | [redacted] | | |
| | Name | Signature | dd-mmm-yyyy |

## TABLE OF CONTENTS

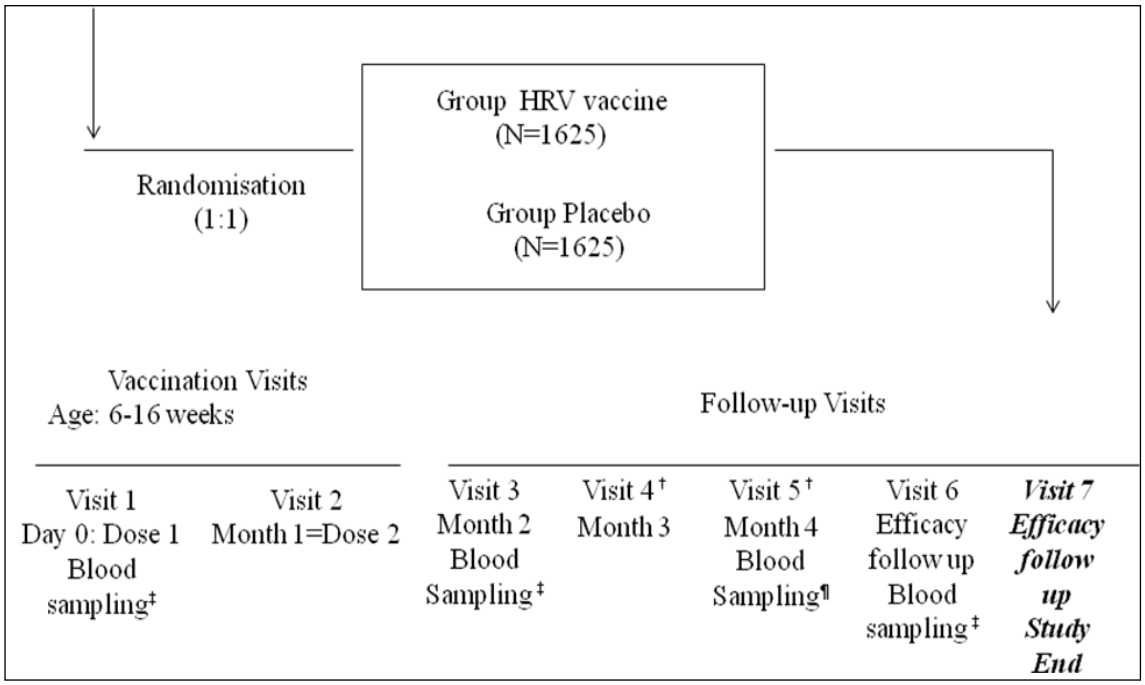
**PAGE**

# 1. DOCUMENT HISTORY

| Date | Version | Description |
|---|---|---|
| 16-Feb-2012 | First Version | First approved version |
| 27-July-2012 | Amendment 1 | Second approved version<br>The changes from the previous version include,<br>• Addition of analysis of efficacy from visit 6 to visit 7.<br>• Change in sequence of analysis to account for the delay in availability of Immuno data during the final analysis. |
| 06-Aug-2012 | Amendment 2 | Third approved version<br>The changes from the previous version include,<br>• Change in ATP cohort definition for co-administered vaccines.<br>• Generation of individual data listings along with the final analysis for all the data except for Immunogenicity data.<br>• The individual data listings for immunogenicity data will be generated as part of the annex analysis |
| 07-May-2013 | Amendment 3 | Fourth approved version<br>The changes from the previous version include,<br>• The ATP cohort used for the analysis of immunogenicity of co-administered vaccines will be called “ATP cohort for immunogenicity – co-administered vaccination”.<br>• An exploratory analysis of efficacy by sero status of subjects against rotavirus IgA at visit 6 will be performed on the efficacy data collected from visit 6 up to visit 7 will be performed.<br>• An analysis summarizing the number of RVGE/Severe RVGE cases reported during the efficacy follow-up classified by the rotavirus IgA status at visit 3 and visit 6 will be performed.<br>• An exploratory analysis of efficacy by sero status of subjects against rotavirus IgA at visit 6 will be performed on the efficacy data collected from visit 6 up to visit 7 will be performed.<br>• The distribution of antibody concentrations at post vaccination time point for each antigen in the co-administered vaccines will be displayed using the RCCs. |

# 2. STUDY DESIGN

The study design for all subjects is as follows:




N: Number of subjects planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort2.
‡Blood will be drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood will be drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 will receive a dose of OPV at Visit 1, Visit 2 and Visit 3; and will receive a dose of DTPa at Visit 2, Visit 3 and Visit 4

- Experimental design: Phase III, double-blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.

- Duration of the study: The subjects will be followed until April 2012 (i.e. end of RV season in China). The intended duration of the study, per subject, will not exceed a maximum of 21 months. The study will have a single epoch as follows.

  – Primary: Primary starting Visit 1 (Day 0) and ending Visit 7 (April 2012 i.e. end of RV season in China).

Table 1 presents the study groups and the epoch foreseen in the study.

**Table 1 Study groups and epochs foreseen in the study**

| Study group | Number of subjects | Age in weeks (MIN/Max) | Epoch |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 – 16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedules: Two oral doses of the liquid HRV vaccine or placebo will be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.

  – Subjects in each group will receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study must be documented in the electronic case report form (eCRF).

- Treatment groups:

  – Group HRV vaccine (N = 1625)
  – Group Placebo (N = 1625)

The treatment groups for the study are presented in Table 2.

**Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine will be given concomitantly with liquid HRV Vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

- Treatment allocation: Randomized with balanced allocation (1:1).

- Blinding**:** Double-blind study.

Table 3 presents the blinding of the study epoch.

**Table 3 Blinding of study epochs**

| Study Epochs | Blinding |
|---|---|
| Primary | double-blind |

- Blood Sampling: Blood samples will be collected from two sub-cohorts of subjects.

  – Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).

  – Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).

  – Immunogenicity sub-cohort 1 & sub-cohort 2 are two different sub-cohorts for immunogenicity.

- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) of liquid HRV vaccine/placebo after each dose, using diary cards (applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).

- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (applicable only for subjects in the immunogenicity sub-cohort 2).

- Unsolicited AEs will be followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV vaccine/placebo.

- Recording of SAEs throughout the study period for all subjects.

  – For subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.

- Active follow-up for occurrence of GE* episodes will be conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE is defined as diarrhoea with or without vomiting.

- For each GE episode occurring during the study period,

  – a GE diary card should be completed daily until end of the GE symptoms.

  – a stool sample should be collected as soon as possible after GE symptoms begin.

  - for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.

- All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).

- The additional informed consent will be taken for the extended follow-up.

- Type of study: self-contained.

- Data collection: eCRF .

- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or at study conclusion, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before study conclusion, an annex report will present all data up to study conclusion.

# 3. OBJECTIVES

## 3.1. Primary objective

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.

  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy (conditional method) is at least 10%

Refer to Section 4.1 for the definition of the primary endpoint.

## 3.2. Secondary objectives

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at visit 6 when co-administered with the routine childhood vaccines
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

Refer to Section 4.2 for the definition of the secondary endpoints.

# 4. ENDPOINTS

## 4.1. Primary endpoint

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

## 4.2. Secondary endpoints

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as GMC at Visit 3 and at Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  - Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

# 5. STUDY POPULATION

A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination. Target enrolment will be 3250 eligible subjects. (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

## 5.1. Total vaccinated cohort

The total vaccinated cohort will include all subjects with at least one dose of the liquid HRV vaccine or placebo administration documented:

- A safety analysis based on the total vaccinated cohort will include all vaccinated subjects,
- An immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects from the immunogenicity sub-cohorts for whom immunogenicity data are available,
- An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available.

## 5.2. According-To-Protocol cohort for analysis of safety

The ATP cohort for safety will include all vaccinated subjects:

- who have received at least one dose of HRV vaccine/Placebo according to their random assignment.
- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol, in the timeframe specified in the protocol.

## 5.3. According-to-protocol cohort for analysis of efficacy

The ATP cohort for efficacy will include all subjects from ATP cohort for safety.

- for whom the randomisation code has not been broken,
- who have not received a vaccine forbidden by or not specified in the protocol, in the timeframe specified in the protocol.
- who have received 2 doses of the liquid HRV vaccine or placebo,
- who have entered the efficacy surveillance period:
  - have follow-up beyond 2 weeks post Dose 2 of study vaccination

– who have no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks post Dose 2 of liquid HRV vaccine or placebo.

## 5.4. According-to-protocol cohort for analysis of efficacy – extended follow-up

The ATP cohort for efficacy – extended follow-up will include all subjects from ATP cohort for efficacy, who have follow-up beyond visit 6(year 1).

## 5.5. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include subjects in the immunogenicity sub-cohorts 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 up to visit 3,
- with no protocol violation of demographics (unknown age at study entry or outside the protocol defined age interval),
- who comply with vaccination schedule of liquid HRV vaccine or placebo,
- who comply with blood sampling schedule till visit 3,
- for whom immunogenicity data was available, at pre and post sampling time-points (at visit 3),
- who have no concomitant infection unrelated to the vaccine up to visit 3, which may influence the immune response,
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 3,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1.

For the analysis of co-administered vaccines (sub-cohort 2) along with the bullet points 1, 2, 3, & 7 the below mentioned criteria will also be considered. ***This cohort will be called "ATP cohort for immunogenicity – co-administered vaccination".***

- who have complete vaccination for OPV & DTPa (all three doses received)
- who comply with vaccination schedule for the co-administered vaccines
- who comply with blood sampling schedule for the analysis of co-administered vaccines (visit 5)

- for whom immunogenicity data was available, at post sampling time-point (visit 5)

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

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 available results are excluded from the ATP cohort for immunogenicity. In such a case, the total vaccinated cohort analyses will evaluate whether exclusion from the ATP cohort could have biased the results.

| Cohort | Elimination codes | Eli Type |
|---|---|---|
| Total vaccinated cohort | 1030 | MA |
| ATP cohort for safety | 1030,1040,1050,1060,1070 | MA |
| ATP cohort for immunogenicity | 1030,1040,1050,1060,1070, 2010, 2020, 2040, 2050, 2060, 2070, 2080, 2090,2100, 2120, 2130 | MA |
| ATP cohort for immunogenicity – ***co - administered vaccination*** | 1030,1040,1050,1060,1070, 2005, 2010, 2020, 2040, 2050, 2060, 2070, 2080, 2090,2100, 2120, 2500 | CO (For the analysis of co-administered vaccines) |
| ATP cohort for efficacy | 1030, 1040, 1050, 1060,1070, 3010, 3020, 3030 | MA |
| ATP cohort for efficacy – extended follow-up | 4020 | MA |

# 6. STATISTICAL METHODS

## 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 and overall. The racial and gender composition will be presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo and at visit 6, at visit 7 will be calculated per group and over all. The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group. The percentages of subjects who received concomitant and intercurrent vaccinations will be tabulated by group & dose.

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

The numbers of subjects who withdrew from the study will be tabulated by group according to the reason for drop-out.

The deviations from specifications for age and intervals between study visits will be tabulated by group.

## 6.2. Analysis of efficacy

The ATP cohort for efficacy will be used for the primary analysis of efficacy. An analysis of efficacy based on the total vaccinated cohort will also be performed.

Vaccine efficacy will be calculated, with their 95% CI against:

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

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

- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains during the efficacy follow-up period.

- any and severe RV GE due to each non-G1 type during the efficacy follow-up period.

- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.

- any and severe all cause GE during the efficacy follow-up period.

- Vaccine efficacy will also be derived from a Cox regression model on the time to first event with censoring for subjects without an event as an additional supportive & exploratory analysis.

- Vaccine efficacy analysis will also be performed on the data collected from 2 weeks post dose 2 of HRV vaccine /placebo up to visit 6. This will be presented as an additional supportive analysis.

The primary objective will be reached if the lower limit of the 95% confidence interval on vaccine efficacy (conditional method) for the HRV group against severe RVGE caused wild-type RV strains during the efficacy follow-up period is >= 10% [Section 7.3].

Vaccine efficacy, derived from a Cox regression model on the time to first event with censoring at the database lock for subjects without event. The model includes the group as fixed effect. This will be performed as an exploratory/supportive analysis. [Kalbfleisch, J. D. and Prentice, R. L. (2002) the *Statistical Analysis of Failure Time Data*: Wiley]

Incidence rate in a group (P) is computed as the number of subjects reporting at least one event (n)/total follow-up time to a first event censored at the database lock date/visit 5 (T). The associated 95% CI's was obtained considering that n follows a Poisson distribution with P*T parameter.

The number of events prevented by 100 vaccinated infant-years will be obtained from 100 times the difference in the incidence rate. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008]. This will be performed as an exploratory/supportive analysis.

An exploratory/supportive analysis of vaccine efficacy by serostatus of subjects against rota virus IgA antibody at visit 3 will be performed***. Similar analysis will be performed considering the serostatus at visit 6 for the efficacy data collected from visit 6 up to visit 7 on ATP cohort for efficacy for second year follow up.***

The above mentioned analysis will also be performed on Total Vaccinated Cohort from dose 1 to study end/database lock & from dose 1 to visit 6/database lock.

An exploratory analysis of efficacy will be performed on the efficacy data collected between visit 6 to visit 7 on the subjects who have follow-up beyond visit 6 (ATP cohort for efficacy - extended follow-up).

***An analysis summarizing the number of RVGE/Severe RVGE cases reported during the efficacy follow-up classified by the rotavirus IgA status at visit 3 and visit 6 will be performed.***

## 6.3. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for the analysis of immunogenicity. If the percent of enrolled subjects excluded from this ATP cohort is more than 5%, a second analysis based on the Total Vaccinated cohort will be performed to complement the ATP analysis.

**For subjects in the immunogenicity sub-cohort 2:**

For each treatment group, anti-D, anti-T, anti-PT, anti-FHA, anti-PRN and anti-poliovirus serotype 1, 2 and 3 at pre-vaccination and at visit 5 will be summarized as follows

- Seroprotection /seropositivity rates and their exact 95% CIs will be calculated [Clopper, 1934].
- GMT/GMCs and their 95% CIs will be calculated.
- ***The distribution of antibody concentrations at post vaccination time point for each antigen will be displayed using the reverse cumulative curves (RCCs).***

**For each sub-cohort 1 & sub-cohort2 and the pooled sub-cohort:**

For each treatment group, anti-rotavirus IgA measured at pre vaccination & at post vaccination will be summarized as follows

- Seroconversion/seropositivity rates and their exact 95% CI will be calculated [Clopper, 1934].
- GMCs and their 95% CI will be calculated.
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the placebo group will be computed [Newcombe, 1998, Method 6].
- The asymptotic standardised 95% CI for difference in the percentage of subjects who are seropositive for anti-rotavirus IgA antibody concentrations at Visit 6 between the HRV vaccine and the placebo group will be computed [Newcombe, 1998, Method 6].

- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 will be displayed using reverse cumulative curves (RCCs).

An exploratory analysis of immunogenicity for anti-rotavirus IgA antibody will be performed by excluding the subjects who took anti viral drugs from dose 1 to visit 3.

***An exploratory analysis summarizing the anti rotavirus IgA seropositivity status and GMCs at visit 6 by excluding the subjects reporting RVGE from dose 1 up to visit 6 will be performed.***

## 6.4. Analysis of safety

Note: Intensity of fever will be assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale will be performed separately.

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.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each dose, for overall doses and per subject. The same calculations will be performed for any grade 3 (solicited or unsolicited) symptoms and for any (solicited or unsolicited) symptom related to vaccination.

The incidence, with exact 95% CI, of each individual solicited general symptom, will be calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects with at least one local AE (solicited and unsolicited) after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination will be tabulated with exact 95% CI. The same calculations will be performed for any grade 3 (solicited or unsolicited) symptoms, grade 3 related symptoms and for any symptoms requiring medical attention.

- The percentage of subjects reporting each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa during the 8-day (Days 0–7) follow-up period with exact 95% CI will be tabulated.
- Occurrence of fever and related fever will be reported per 0.5°C cumulative temperature increments.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

**For all subjects:**

The incidence, with exact 95% CI, of each individual solicited general symptom common to both the sub-cohorts, will be calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

SAEs reported during the study period (i.e. from first vaccine dose till study end) will be described in detail.

# 7. STATISTICAL CALCULATIONS

## 7.1. Derived and transformed data

**Demography**

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

**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.

The subjects, who have completed Visit 6 and have not given their consent to participate in the extension follow-up, will be considered as dropouts from the study. The ATP cohort for the analysis of efficacy will include all the subjects who have satisfied the points mentioned in the section 5.3.

**Immunogenicity**

The cut-off value is defined by the laboratory before the analysis.

- 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. The following seropositivity thresholds are applicable:

  – Anti-PT and anti-FHA antibody concentrations Greater than or equal to ≥ 20 El.U/ml

  – Anti-PRN should be at least a 4-fold increase in antibody concentration for the ratio of post-vaccination to pre-vaccination

  – Anti rotavirus IgA antibody concentration ≥ to 20 U/mL

- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:

  – Anti-diphtheria antibody concentrations ≥ 0.1 IU/ml.

  – Anti-tetanus antibody concentrations ≥ 0.1 IU/ml.

  – Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8.

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

- The GMCs calculations are performed by taking the anti-log of the mean of the log concentrations 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 the immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

**Safety/Reactogenicity**

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

## 7.2. Data presentation description

The following decimal description will be used for the demography, efficacy, reactogenicity and immunogenicity analyses.

| **Display Table** | **Parameters** | Number of decimal digits |
|---|---|---|
| All summaries | % of count, including LL & UL of CI | 1 |
| All summaries | % of difference, including LL & UL of CI | 2 |
| All summaries | p-value | 3 |
| Demographic characteristics | Mean, median age | 1 |
| Demographic characteristics | SD (age) | 2 |
| Immunogenicity | GMC for Rota virus IgA antibody | 1 |
| Immunogenicity | GMC for anti-PRP, anti-Diphtheria, anti-Tetanus | 3 |
| Immunogenicity | GMC for anti-PT, anti-FHA, anti-PRN and GMT for anti-polio type 1,2,3 | 1 |

| | | |
|---|---|---|
| Efficacy | % VE including LL & UL | 1 |
| Efficacy | % of difference, including LL & UL of CI | 2 |

## 7.3. Methodology for computing CI

All CI will be 2 sided 95% CI.

- The 95% CI for geometric mean concentrations (GMCs) will be obtained within each group separately. The 95% CI for the mean of log-transformed concentration will be first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMCs will be then obtained by exponential-transformation of the 95% CI for the mean of log-transformed concentration.
- The Vaccine Efficacy (VE) will be estimated as 1 – the relative risk. The same transformation will be used to derive the exact CI boundaries from those obtained for the relative risk. The CI for the the relative risk will be based on the method C 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

# 8. CONDUCT OF ANALYSES

Any deviation(s) or change(s) from the original statistical plan outlined in this SAP will be described and justified in the final study report.

## 8.1. Sequence of analyses

Final analysis will be done when 40 severe RV GE cases caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or at study conclusion, whichever is the earliest.

If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before study conclusion,

- The final analysis (case triggered analysis) will be run by an independent analysis centre in order to preserve blinding as much as possible. No individual data listing will be generated during this analysis. However, due to regulatory requirements associated with the clinical report, fatalities and drop-out will be unblinded. In addition, planned summaries may lead to inadvertent unblinding.

- An annex report will present all data up to the study conclusion. The annex report will not be used to conclude on the study objectives. The analysis of the annex report will be complementary /descriptive.

Immunogenicity analysis will be included in the last report.

Or

If efficacy analysis at study conclusion,

- The final analysis will present the efficacy, safety & reactogenecity data collected from dose 1 of HRV/Placebo up to visit 7 and this analysis will be run by GSK statistician. All individual data listings except for immunogenicity data will be presented along with this reported.

- An annex report will present the immunogenicity data collected during the study. This analysis will present the individual data listings for immunogenicity data.

| **Description** | **Analysis ID (SDD sub-folder)** | **TFL short title** |
|---|---|---|
| | | |
| If 40 severe RVGE cases are reported before the last visit of end of efficacy follow up | | |
| Case Triggered Analysis | ANALYSIS_E1_03 (CTANALYSIS) | Case Triggered Analysis |
| AND | | |
| Annex Analysis | ANALYSIS_E1_04 (ANNEX) | Annex Analysis |
| OR(final analysis at study conclusion) | | |
| Final Analysis | ANALYSIS_E1_02 (FINAL) | Final Analysis |
| AND | | |
| Annex Analysis* | ANALYSIS_E1_03 (ANNEX) | Annex Analysis |

* This annex report will present the immunogenicity data collected in the study.

## 8.2. Statistical considerations for interim analyses

No interim analysis is planned for the study.

# 9. CHANGES FROM PLANNED ANALYSES

Following exploratory analysis is included in the analysis of Immunogenicity,

- An exploratory analysis of immunogenicity for anti-rotavirus IgA antibody will be performed by excluding the subjects who took anti viral drugs from dose 1 to visit 3.

- ***An exploratory analysis summarizing the anti rotavirus IgA seropositivity status and GMCs at visit 6 by excluding the subjects reporting RVGE from dose 1 up to visit 6 will be performed.***

- ***The distribution of antibody concentrations at post vaccination time point for each antigen in the co-administered vaccines will be displayed using the RCCs.***

Following exploratory analysis is included in the analysis of Efficacy,

- An exploratory analysis of efficacy will be performed on the efficacy data collected between visit 6 to visit 7 on the subjects who have follow-up beyond visit 6 (ATP cohort for efficacy - extended follow-up).

- ***An exploratory analysis of efficacy by sero status of subjects against rotavirus IgA at visit 6 will be performed on the efficacy data collected from visit 6 up to visit 7 will be performed. This will be presented in the Annex report.***

- ***An analysis summarizing the number of RVGE/Severe RVGE cases reported during the efficacy follow-up classified by the rotavirus IgA status at visit 3 and at visit 6 will be performed. This will be presented in the Annex report.***

# 10. REFERENCES


- Kalbfleisch, J. D. and Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data*: Wiley.

- Construction of confidence limits about effect measures: A general approach, by G. Y. Zou and A. Donner, *Statistics in Medicine* 2008; 27:1693–1702

- Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413

- Robert G. Newcombe, Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods, *Statist. Med.* 17, 873-890 (1998), Method 6.

# 11. ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ATP** | According-To-Protocol |
| **CI** | Confidence Interval |
| **GMC** | Geometric mean antibody concentration |
| **GSK** | GlaxoSmithKline |
| **IU/ml** | International units per milliliter |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **SAP** | Statistical Analysis Plan |
| **DTPa** | Diphtheria, Tetanus, acellular Pertussis vaccine |
| **eCRF** | electronic Case Report Form |
| **EPI** | Expanded Program of Immunisation |
| **FHA** | Filamentous Haemagglutinin |
| **GE** | Gastroenteritis |
| **HRV** | Human Rotavirus |
| **IgA** | Immunoglobulin A |
| **LAR** | Legally Acceptable Representative |
| **mL** | Millilitre |
| **O** | Oral |
| **OPV** | Oral Poliovirus vaccine |
| **PRN** | Pertactin |
| **PT** | Pertussis toxid |
| **RV** | Rotavirus |
| **SAE** | Serious Adverse Event |
| **U/mL** | Units per Millilitre |
| **VE** | Vaccine Efficacy |

# GlaxoSmithKline Biologicals
# Global Clinical Research and Development
# Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Final Study Report, including appendices

STUDY TITLE: Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants

Study: 113808 (ROTA-075) Development Phase: III

*I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Clinical Development,
Combination Vaccines
(Infanrix/Boostrix/Hepatitis) and Rotavirus
Vaccines, Global Vaccine Development
GlaxoSmithKline Biologicals

Signature: [redacted]

Date: 8 NOV 2012

For internal use only

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# GlaxoSmithKline Biologicals

## Study title

Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants.

## Study detailed title

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

# Annex Clinical Study Report for Study 113808 (ROTA-075)

**Development Phase** III

**IND Number: 2009L10238**

**Indication Studied:** Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

| | |
|---|---|
| **Study initiation date:** | 29 August 2010 |
| **Study completion date:** | 12 May 2012 |
| **Data lock point (Date of database freeze for immunogenicity):** | 07 June 2013 |
| **Date of annex report:** | Final: 08 August 2013 |
| **Report Scope:** | This clinical study report presents the immunogenicity results of HRV vaccine and co-administered routine childhood vaccines, in a subset of the population enrolled in the study. |
| **Earlier Study Reports** | Report 29-Oct-2012 |

**Sponsor Signatory:** [redacted] MBBS
Director, Lead Clinical Development,
DTP Combination Vaccines and Rotavirus Vaccines,
Late Clinical Development
GlaxoSmithKline Biologicals.

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

*GSK Biologicals' Study Report INS-BIO-CLIN-1010 v04*

# Foreword

**Study title**

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid HRV vaccine in healthy Chinese infants.

**Name of the Investigational Product:** GSK Biologicals' oral live attenuated HRV vaccine (Rotarix™).

**Name of the Sponsor:** GSK Biologicals, Rixensart, Belgium.

| | |
|---|---|
| **Study Start Date** | 29 August 2010 |
| **Study End date** | 12 May 2012 |

**Name of the Principal Investigator:** Dr. [redacted]

**Address of the Study centre (PI):** [redacted] China.

**Date of the study report**: 08 August 2013

| | |
|---|---|
| **Name of the Sponsor contacts at GSK:** | [redacted]<br>Director, Lead Clinical Development,<br>DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development<br>GlaxoSmithKline Biologicals. |

**Storage of source documents pertaining to the study:**

| | |
|---|---|
| **At the Investigator site:** | [redacted] China |
| **At GSK China:** | 19, Shunchi Road, Beijing Airport Logistics Zone, Shunyi Distric, Beijing, 101300, China. |
| **At GlaxoSmithKline Biologicals:** | Clinical Record Management<br>Archiving Team_WN23-F0-054<br>GlaxoSmithKline Biologicals<br>Avenue Fleming, 20, 1300 Wavre<br>Belgium |

**Summary of the Report: Please refer to the** SYNOPSIS (REPORT SUMMARY)**.**

# SYNOPSIS (REPORT SUMMARY)

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

**Study No.:** 113808 (ROTA-075)

**Title of the study:** A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

**Principal investigator**: Dr. [redacted] was the principal investigator for the study.

**Study Centres:** This study was conducted at 4 centres in China.

**Publication (reference):** Not published as of 08 August 2013

| | |
|---|---|
| **Study period:**<br>**Study initiation date:** 29 August 2010<br>**Study completion date:** 12 May 2012<br>**Data lock point (date of database freeze for immunogenicity):** 07 June 2013 | **Phase:** III |

**Indication:** Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

**Treatment:**

The study groups were as follows:

- Group HRV vaccine (Planned, N = 1625)
- Group Placebo (Planned, N = 1625)

Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.

There were two sub-cohorts in this study as described below.

- Immunogenicity sub-cohort 1 (N=600): To evaluate the immunogenicity of the liquid HRV vaccine.
- Immunogenicity sub-cohort 2 (N=300): To evaluate the immunogenicity of the liquid HRV vaccine and co-administered vaccines.

Subjects in each group were allowed to receive routine childhood vaccinations according to the expanded programme of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 received DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose.

**Objectives:** The study objectives considered for analyses presented in this study report are listed below. Efficacy, reactogenicity and safety objectives were presented in a separate study report (ROTA-075) dated 29-Oct-2012.

***Secondary objectives:***

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and

| **Name of company**: **GlaxoSmithKline Biologicals, Rixensart, Belgium** **Name of finished product:** Liquid HRV Vaccine **Name of active substance:** RIX4414 vaccine strain | **TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:** | **(for national authority only)** |
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seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.

- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

**Study design:**

The study was a double-blind, randomised, placebo controlled, multi-centre study in China with two parallel groups (Group HRV and Group Placebo). Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1. The study comprised of 7 visits [Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2), Visit 4 (Month 3), Visit 5 (Month 4), Visit 6 (at approximately 1 year of age) and Visit 7 (at approximately 20 months of age) at end of the rotavirus season in China (approximately April 2012)]. Blood samples were to be collected from the sub-cohorts as follows:

- **Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600):**
  - Three blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1, Visit 3 and Visit 6.
- **Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300)**:
  - Four blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1, Visit 3, Visit 5 and Visit 6.

Active follow-up for the occurrence of GE* episodes was conducted during the study period via telephone contact or by other means (at least every 2 weeks).

*Note: GE was defined as diarrhoea# with or without vomiting.

# Diarrhoea is defined as three or more looser than normal stools within a day.

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

***Vaccination schedule /site:*** Subjects were to receive two oral doses of liquid HRV vaccine according to a 0, 1 month schedule.

***Vaccine composition /dose /lot number:*** Each 1.5 ml dose of GSK Biologicals' liquid HRV vaccine contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$) of RIX4414 HRV strain, 2.26 mg of Dulbecco's Modified Eagle Medium, 132.74 mg of Di-sodium Adipate and 55% of sucrose (w/w). Lot number AROLA219B, [Expiry date: 30 September, 2012] was used for the liquid HRV vaccination.

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

***Vaccination schedule /site:*** Subjects were to receive two oral doses of the placebo according to a 0, 1 month schedule.

***Vaccine composition /dose /lot number:*** Each 1.5 ml dose of GSK Biologicals' placebo contained 2.26 mg of DMEM, 132.74 mg of Di-sodium Adipate and 55% of sucrose (w/w). Lot number PROLA008A, [Expiry date: (31 October 2012)] was used for the placebo.

**Routine vaccines, dose and mode of administration, lot no.:**

***Vaccination schedule /site:*** Subjects in the immunogenicity sub-cohort 2 were to receive three doses of combined Diphtheria-tetanus- acellular pertussis (DTPa) vaccine as intramuscular injections in the anterolateral thigh at Visits 2, 3 and 4.

***Vaccine composition /dose /lot number:*** Each 0.5 ml dose of GSK Biologicals' DTPa vaccine (*Infanrix*) contained Diphtheria toxoid ≥ 30 international units (IU) [25 Limits of flocculation (Lf)], Tetanus toxoid ≥ 40 IU (10Lf), Pertussis toxoid 25 µg, Filamentous haemagglutinin 25 µg, Pertactin 8 µg, Aluminium as salts 0.5 mg and 2-phenoxyethanol ≤ 2.5 mg. Lot number (YC14B113AA), [Expiry date: 01 July,

| **Name of company**: **GlaxoSmithKline Biologicals, Rixensart, Belgium** **Name of finished product:** Liquid HRV Vaccine **Name of active substance:** RIX4414 vaccine strain | **TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:** | **(for national authority only)** |
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2012] was used for the DTPa vaccination.
***Vaccination schedule /site:*** Subjects in the immunogenicity sub-cohort 2 were to receive three oral doses of Oral poliovirus vaccine (OPV) vaccine at Visits 1, 2 and 3.
***Vaccine composition /dose /lot number:*** Each dose of 0.1 ml (2 drops) of Institute of Medical Biology Chinese Academy of Medical Sciences' OPV contained Total polio-virus not less than 6.15 $lgCCID_{50,}$ type 1 not less than 6.0 $lgCCID_{50}$, type 2 not less than 5.0 $lgCCID_{50}$, type 3 not less than 5.5 $lgCCID_{50}$. Lot number [20100202], [Expiry date: 01 February, 2012] was used for the OPV vaccination.

**Study Population:**
The study population included healthy male/ female infants of Chinese origin aged between 6 and 16 weeks (42-112 days) at the time of the first vaccination who were born after a gestation period of 36 to 42 weeks inclusive. Written informed consent was obtained from the parents/legally acceptable representatives (LARs) of these subjects.

**Duration of treatment:**
The duration of the study, per subject, did not exceed a maximum of 21 months.

The study endpoints considered for analyses presented in this study report are listed below.
**Secondary Outcome/Efficacy Variable:**
*Immunogenicity*
*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects).*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as GMCs at Visit 3 and Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  - Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

**Statistical methods:**
***Analysis of Immunogenicity:***
The primary analysis was based on the ATP cohort for the analysis of immunogenicity. As the percentage of enrolled subjects excluded from this ATP cohort was more than 5%, a secondary analysis based on the Total Vaccinated cohort was performed to complement the ATP analysis.
**For subjects in the immunogenicity sub-cohort 2:**
For each treatment group, anti-D, anti-T, anti-PT, anti-FHA, anti-PRN and anti-poliovirus serotype 1, 2 and 3 at pre-vaccination and at Visit 5 was summarized as follows:

- Seroprotection /seropositivity rates and their exact 95% CIs was calculated.
- GMT/GMCs and their 95% CIs were calculated.
- The distribution of antibody concentrations at post-vaccination time point for each antigen was displayed using the reverse cumulative curves (RCCs).

**For each sub-cohort 1 and sub-cohort 2 and the pooled sub-cohort:**
For each treatment group, anti-rotavirus IgA antibody measured at pre-vaccination & at post-vaccination time points were summarized as follows:

- Seroconversion/seropositivity rates and their exact 95% CI were calculated.

| **Name of company**: **GlaxoSmithKline Biologicals, Rixensart, Belgium** **Name of finished product:** Liquid HRV Vaccine **Name of active substance:** RIX4414 vaccine strain | **TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:** | **(for national authority only)** |
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- GMCs and their 95% CI were calculated.
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the Placebo group were computed.
- The asymptotic standardised 95% CI for difference in the percentage of subjects who are seropositive for anti-rotavirus IgA antibody concentrations at Visit 6 between the HRV vaccine and the Placebo group were computed.
- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 was displayed using reverse cumulative curves (RCCs).

An exploratory analysis of immunogenicity for anti-rotavirus IgA antibody was performed by excluding the subjects who took anti viral drugs from dose 1 to Visit 3.

An exploratory analysis summarizing the anti-rotavirus IgA antibody seropositivity status and GMCs at Visit 6 by excluding the subjects reporting RVGE from Dose 1 up to Visit 6 was performed.

**Summary:**

***Immunogenicity:***

***Anti-rotavirus IgA antibody response***

Immunogenicity sub cohort 1:

- Anti-rotavirus IgA seroconversion rate was 74.7% [95% CI: 68.9%; 79.9%] in the HRV group one month post-Dose 2 of HRV vaccination. Anti-rotavirus IgA seropositivity rate was 3.5% [95% CI: 1.6%; 6.6%] in the Placebo group one month post-Dose 2 of placebo.
- Anti-rotavirus IgA antibody GMCs in overall subjects were 90.2 U/ml [95% CI: 73.3; 111.1] in the HRV group and < 20 U/ml in the placebo group, one month post-Dose 2 of HRV vaccine/placebo.
- Anti-rotavirus IgA antibody seropositivity rate was 71.5% [95% CI: 65.5%; 77.1%] in the HRV group at approximately one year of age. Anti-rotavirus IgA seropositivity rate was 46.8% [95% CI: 40.5%; 53.2%] in the Placebo group, at approximately one year of age.
- Anti-rotavirus IgA antibody GMCs in overall subjects were 66.5 U/ml [95% CI: 54.6; 81.0] in the HRV group and 35.3 U/ml [95% CI: 29.3; 42.5] in the placebo group, at approximately one year of age.

Immunogenicity sub cohort 2:

- Anti-rotavirus IgA antibody seroconversion rate was 64.2% (95% CI: 55.4%; 72.3%) in the HRV group, one month post-Dose 2 of HRV vaccine. Anti-rotavirus IgA seropositivity rate was 9.4% (95% CI: 5.1%; 15.5%) in the Placebo group one month post-Dose 2 of placebo.
- Anti-rotavirus IgA antibody GMCs in overall subjects was 84.0 U/ml [95% CI: 58.9; 119.8] in the HRV group and < 20 U/ml in the placebo group, at one month post-Dose 2 of HRV vaccine/placebo.
- Anti-rotavirus IgA antibody seropositivity rate was 50.0% (95% CI: 40.9%; 59.1%) in the HRV group, at approximately one year of age. Anti-rotavirus IgA seropositivity rate was 21.8% (95% CI: 15.1%; 29.8%) in the Placebo group, at approximately one year of age.
- Anti-rotavirus IgA antibody GMCs were 31.3 U/ml [95% CI: 24.6; 39.8] in the HRV group and <20 U/ml in the placebo group, at approximately 1 year of age.

***Antibody response to diphtheria toxoid and tetanus toxoid***

- The anti-diphtheria and anti-tetanus antibody seroprotection rates (defined as antibody concentrations ≥ 0.1 IU/ml) at one month post-Dose 3 of DTPa vaccine was 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group.
- At one month post-dose 3 of DTPa vaccine, the anti-diphtheria antibody GMCs in overall subjects reported for the HRV group was 0.375 IU/ml [95% CI: 0.326; 0.432] and for the Placebo group was 0.334 IU/ml [95% CI: 0.308; 0.363].

| **Name of company**: **GlaxoSmithKline Biologicals, Rixensart, Belgium** **Name of finished product:** Liquid HRV Vaccine **Name of active substance:** RIX4414 vaccine strain | **TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:** | **(for national authority only)** |
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- At one month post-dose 3 of DTPa vaccine, the anti-tetanus antibody GMCs in overall subjects reported for the HRV group was 1.281 IU/ml [95% CI: 1.253; 1.309] and for the Placebo group was 1.343 IU/ml [95% CI: 1.215; 1.486].

***Antibody response to PT, FHA and PRN***

- The anti-PT, anti-FHA, and anti-PRN antibody seropositivity rates (defined as antibody concentrations ≥ 5 EL.U/ml) were 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, at one month post-Dose 3 of DTPa vaccine.
- At one month post-dose 3 of DTPa vaccine, the anti-PT antibody GMCs reported for the HRV group was 88.9 U/ml [95% CI: 84.9; 93.2] and for the Placebo group was 90.5 U/ml [95% CI: 86.4; 94.8].
- At one month post-dose 3 of DTPa vaccine, the anti-FHA antibody GMCs reported for the HRV group was 59.5 U/ml [95% CI: 55.8; 63.5] and for the Placebo group was 65.8 U/ml [95% CI: 61.3; 70.5].
- At one month post-dose 3 of DTPa vaccine, the anti-PRN antibody GMCs reported for the HRV group was 41.9 U/ml [95% CI: 37.6; 46.5] and for the Placebo group was 50.8 U/ml [95% CI: 44.3; 58.1].

***Antibody response to poliovirus types 1, 2 and 3***

- Anti-poliovirus type 1 and 2 seroprotection rates (defined as antibody titres ≥ 8 ED50) were 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, two months post-Dose 3 of OPV vaccine.
- Anti-poliovirus type 3 seroprotection rate (defined as antibody titres ≥ 8 ED50) was 99.3% [95% CI: 96.0%; 100%] in the HRV group and 99.3% [95% CI: 96.1%; 100%] in the placebo group, two months post-Dose 3 of OPV vaccine.
- At two months post-dose 3 of OPV vaccine, the anti-Polio 1 antibody GMTs reported for the HRV group was 2101.1 [95% CI: 1734.8; 2544.8] and for the Placebo group was 2259.4 [95% CI: 1844.4; 2767.9].
- At two months post-dose 3 of OPV vaccine, the anti-Polio 2 antibody GMTs reported for the HRV group was 402.5 [95% CI: 334.8; 483.9] and for the Placebo group was 425.1 [95% CI: 371.0; 487.1].
- At two months post-dose 3 of OPV vaccine, the anti-Polio 3 antibody GMTs reported for the HRV group was 426.6 [95% CI: 342.7; 531.0] and for the Placebo group was 360.3 [95% CI: 303.0; 428.3]

**Conclusion:**

- Two doses of GSK Biologicals' oral live attenuated liquid HRV vaccine was immunogenic in Chinese infants as evidenced by the anti-rotavirus IgA antibody seroconversion rate and GMCs at one month post Dose 2. The immune response persisted at one year of age as shown by the anti-rotavirus IgA antibody seropositivity rate and GMCs at approximately one year of age.
- Two doses of GSK Biologicals' oral live attenuated liquid HRV vaccine did not appear to impact the immunogenicity of the co-administered DTPa vaccine and Oral Poliovirus vaccine [OPV].

**Date of annex report:** Final: 08 August 2013

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MODULAR APPENDICES

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ATP** | According-To-Protocol |
| **$CCID_{50}$** | Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells) |
| **CI** | Confidence Interval |
| **DMEM** | Dulbecco's Modified Eagle Medium |
| **DTPa** | Combined Diphtheria, Tetanus and acellular Pertussis vaccine |
| **eCRF** | electronic Case Report Form |
| **$ED_{50}$** | Estimated dose 50% |
| **EL.U/mL** | ELISA Units per Millilitre |
| **ELISA** | Enzyme Linked Immunosorbent Assay |
| **EPI** | Expanded Program on Immunisation |
| **FHA** | Filamentous Haemagglutinin |
| **GCP** | Good Clinical Practice |
| **GE** | Gastroenteritis |
| **GMC** | Geometric Mean Concentration |
| **GSK** | GlaxoSmithKline |
| **GSM** | Global Study Manager |
| **HRV** | Human Rotavirus |
| **IB** | Investigator Brochure |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IgA** | Immunoglobulin A |
| **IM** | Intramuscular |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **IS** | Intussusception |
| **IU/mL** | International Units per Millilitre |
| **LAR** | Legally Acceptable Representative |
| **MedDRA** | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| **Mg** | Milligram |
| **mL** | Millilitre |
| **MMWR** | Morbidity and Mortality Weekly Report |
| **NIFDC** | National Institute for Food and Drug Control |
| **O** | Oral |
| **OPV** | Oral Poliovirus vaccine |
| **PCR** | Polymerase Chain Reaction |
| **PRN** | Pertactin |
| **PT** | Pertussis toxoid |
| **RV** | Rotavirus |
| **SAE** | Serious Adverse Event |
| **SAS** | Statistical Analysis System |
| **SBIR** | Internet Randomisation tool |
| **SDV** | Source Document Verification |
| **CFDA** | China Food and Drug Administration |
| **SPM** | Study Procedures Manual |
| **U/mL** | Units per Millilitre |
| **UA** | Upper Arm |
| **UMV** | Universal Mass Vaccination |
| **VE** | Vaccine Efficacy |
| **WHO** | World Health Organisation |

## GLOSSARY OF TERMS

| | |
|---|---|
| **According-To-Protocol cohort:** | This cohort included all subjects enrolled in the study who meet the criteria defined in the protocol for the considered analysis (Efficacy, reactogenicity and safety). |
| **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. 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. The level of blinding was maintained throughout the conduct of the trial, and only when the data were cleaned to an acceptable level of quality appropriate personnel unblinded or when required in case of a serious adverse event (SAE). |
| **Child in care:** | A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted nor has an appointed legal guardian. |
| **Completed:** | Subjects who were available for the study concluding visit. |
| **Diary card:** | Cards given to the parents /guardians by the investigator to record adverse events following vaccination. |
| **Eligible:** | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |
| **Epoch:** | An epoch was a self-contained set of consecutive time-points or a single time-point from a single protocol. Self-contained meant that data collected for all subjects at all time-points within that epoch allowed to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety. |

| | |
|---|---|
| **eTrack:** | GSK's tracking tool for clinical trials. |
| **Evaluable:** | Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis. |
| **Investigational vaccine:**<br><br>**(Synonym of Investigational Medicinal 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. |
| **Legally Acceptable Representative:** | ICH GCP defines Legally Accepted Representative (LAR) as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. |
| **Protocol amendment:** | The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study. |
| **Randomisation:** | Process of random attribution of treatment to subjects in order to reduce bias of selection. |
| **Sub-cohort:** | A group of subjects for whom specific data are collected compared to other subjects. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Subject:** | Term used throughout the clinical study report to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control. |
| **Total vaccinated cohort:** | The total vaccinated cohort will include all subjects with at least one vaccine administration documented. A safety analysis based on the total vaccinated cohort will include all vaccinated subjects. An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available. |

**Treatment number:** A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

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

## TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the Study Report (including the synopsis), the names of the vaccines/products and/or medications will be written without the superscript symbol ™ and in *italics*.

| Trademarks of the GlaxoSmithKline group of companies | Generic description |
|---|---|
| Rotarix™ | Human rotavirus vaccine |
| Infanrix™ | Combined diphtheria-tetanus-acellular pertussis (DTPa) vaccine |

| Trademarks not owned by the GlaxoSmithKline group of companies | Generic description |
|---|---|
| OPV (Institute of Medical Biology, Chinese Academy of Medical Sciences') | Poliomyelitis (live) Vaccine (Monkey Kidney Cell), Oral |

# 1. ETHICS

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

The study protocol, two amendments, the informed consent, and other information that required pre-approval were reviewed and approved by an investigational centre IEC.

## 1.2. Ethical conduct of the study

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

## 1.3. Subject information and consent

Written informed consent was to be obtained from the parent/ legally acceptable representative (LAR) prior to the performance of any study-specific procedures. Electronic case report forms (eCRFs) were provided for each subject's data to be recorded.

# 2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE (STUDY MANAGEMENT)

## 2.1. Administrative structure

This study was conducted by Dr. [redacted] as the principal investigator in four centres in China.

**Responsibilities of the Investigator:**

- Compliance with GCP procedures and applicable local regulations in China.
- Permitting monitoring and auditing by GSK Biologicals or a GSK Biologicals' designated organisation.
- Maintenance of a list of appropriately qualified persons to whom trial-related duties were delegated to.

In terms of the Investigator resources *([International Conference on Harmonisation] ICH-GCP 4.2)*:

- Potential for recruiting potential subjects
- Sufficient time to conduct the trial
- Qualified personnel and adequate training of study personnel

- Adequate facilities at the study centre to conduct the trial.

In terms of obtaining approval from the appropriate IRB/ IEC *(ICH-GCP 4.4)*:

Before initiating the trial, the Investigator had written and dated approval for:

- The trial protocol
- Written informed consent form and consent form updates (if any)
- Subject recruitment procedures (e.g., advertisements)
- Any other information that was to be provided to the subjects
- Investigator brochure.

In terms of medical care of trial subjects *(ICH-GCP 4.3)*:

- A qualified physician (Investigator or sub-investigator) was responsible for all trial-related medical decisions.

In terms of compliance with the protocol *(ICH-GCP 4.5):*

- The Investigator/ Institution signed the protocol, or an alternative contract, to confirm agreement to comply with the protocol and was not to implement any deviations without:
  - agreement by the Sponsor
  - prior review and documented approval from the IRB/ IEC of an amendment
  - except, where necessary to eliminate an immediate hazard(s) to trial subjects or
  - when changes involved only logistical or administrative aspects of the trial.

In terms of accountability of the investigational product *(ICH-GCP 4.6)*:

- Accountability of the investigational product at the trial site was the sole responsibility of the Investigator, for which the Investigator maintained adequate documentation that:
  - doses were provided to subjects as specified in the protocol
  - reconciliation of all investigational products received from the Sponsor
  - the investigational product was to be stored and used as specified in the protocol.

In terms of maintenance of trial-related records and reports *(ICH-GCP 4.9.5)*:

- Records were accurate, complete, legible and timely pertinent to the data reported (i.e. subjects' hospital records, eCRFs)
- Data reported on the eCRFs were derived from the source document

- All corrections to a eCRF were dated, initialed, explained and were not to obscure the original entry

**Note**: eCRFs were used in this study and the Remote Data Entry (RDE) application used an in-built system to track any corrections to data.

- The period of retention of all documents will be a minimum of two years after the last approval of marketing application of the product
- The Investigator is to permit direct access to all trial-related records and reports to the Sponsor (auditor, monitor), IRB/ IEC and regulatory authorities.

In terms of communication with the IRB/ IEC:

During trial period, investigator forwarded to the IRB/IEC:

- Investigator brochure updates
- written summaries on the status of the trial annually or more frequently (if it was requested)
- The Investigator was to provide written progress reports to the Sponsor and the IRB/ IEC on any changes that significantly affected the trial or increased risk to subjects.

If the Investigator terminated or suspended the trial without prior agreement of the Sponsor, the Investigator was to provide detailed written explanation to the Sponsor, the IRB/ IEC and the regulatory authorities (if required).

In case of premature termination or suspension of a trial the Investigator was to inform trial subjects and assure appropriate therapy and follow-up.

After completion of the trial, the Investigator was to inform and provide the Sponsor and the IRB/ IEC all the required reports, a summary of the study outcome and reports to regulatory authorities (if applicable).

Additionally, the Investigator was also responsible for:

- The review of the consent form and appropriate consent procedure *(ICH-GCP 4.8)*
- Reporting of serious adverse events (SAEs) to Sponsor and the IRB/ IEC and notification of investigator brochure updates to IRB/ IEC *(ICH-GCP 4.11)*.

**Responsibilities of the Study Sponsor:**

GSK Biologicals, Rixensart, Belgium is the study Sponsor and was responsible for administration of the study including clinical trial supply management.

In terms of implementing and maintaining Quality Assurance (QA) and Quality Control (QC) systems:

- The Sponsor was to ensure that the trial was conducted, data generated and documentation of data (data were reliable and processed correctly) and reported data were in compliance with the protocol, GCP and regulatory requirements.
- The Sponsor was to secure a written agreement with the Investigator (institution and/ or parties involved in the clinical trial) to the trial-related site, source data/ documents and reports, primarily for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.
- If the Sponsor was to transfer any trial-related duties and functions to a clinical research organization (CRO), it was the Sponsor's responsibility to ensure:
  - quality and integrity of trial data. It was the function of the CRO to implement QA and QC
  - clear explanation of functions that were "not" transferred to the CRO, including the duties and functions of the Sponsor.
- The Sponsor was to designate qualified medical personnel to answer any trial-related medical queries. The Sponsor was also to appoint qualified personnel (biostatisticians, physicians etc) for:
  - designing protocols and eCRFs, analysing data, and for preparation of clinical trial reports/ study reports.
  - supervision of the trial and handling and verification of data.
- The Sponsor was to provide guidance to the Investigator on the clinical trial protocol and protocol amendments, including ICH guidance on the structure of the clinical trial.
- For trial management, the Sponsor was to provide Subject Identification Code and retain all Sponsor-specific essential documents.
- In case of discontinuation (termination/ suspension) of the clinical trial, the Sponsor was to provide a written explanation to the Investigator and the IRB/ IEC.
- In case of transfer of ownership of the trial, the Sponsor was to report this to the relevant authority.
- The Sponsor was to inform the Investigator/ Institution that all trial-related documents were to be retained for a minimum of two years after the last approval of marketing application of the investigational product. The Sponsor was also to inform the Investigator/ Institution regarding the destruction of any documents.

- In terms of selection of the Investigator/ Institution for the trial, the Sponsor was to:
  - select qualified personnel (with experience and resources to conduct the trial). For multicentre trials, the Sponsor was to select a coordinating committee and/ or coordinating investigator(s)
  - provide the protocol and the investigator brochure (that included non-clinical/ clinical data)
  - obtain the Investigator's/ Institution's agreement to conduct the trial according to GCP (after obtaining approval from the IRB/ IEC), to comply with procedures, to permit monitoring, auditing and inspection and to retain essential documents.
- All trial-related duties and functions were to be defined and established by the Sponsor.
- In terms of providing compensation to the subjects and Investigators, the Sponsor was to:
  - provide insurance against claims arising from the trial (except for malpractice and/ or negligence)
  - address costs of treatment (of subjects) i.e. during trial-related injuries
  - compensation of trial subjects in compliance with applicable regulatory requirement(s).
- The Sponsor was to inform the Investigator/ Institution of all financial aspects related to the trial in an agreement.
- The applications required for the trial were to be submitted/ notified by the Sponsor to the appropriate authority(ies) for review, acceptance and/ or for permission to start the trial.
- For confirmation of review of relevant documents by the IRB/ IEC, the Sponsor was to obtain the name and address of the IRB/ IEC, if it operated according to GCP and the applicable laws and regulations in the country. The Sponsor was to ensure that there was documentation for the IRB/ IEC approval for the protocol, written informed consent form(s), written information provided to subjects, subject recruiting procedures, and documents related to payments.
- The Sponsor was to obtain from Investigator/ Institution a copy of the modification(s) made and the approval date given by the IRB/ IEC.
- The Sponsor was to ensure that the investigational product was manufactured according to Good Manufacturing Practices with appropriate coding and labeling of products to maintain blinding and identification.
- The Sponsor was to ensure that the investigational product was sent to the investigational site(s) after obtaining appropriate documentation.
- The Sponsor was to ensure that the Investigator/ Institution maintained the investigational product under defined storage conditions.

- The Sponsor was to provide written procedures to the Investigator/ Institution for the adequate and safe receipt, handling, storage, and dispensing, retrieval of unused investigational product, and return of unused investigational product to the Sponsor (or alternative disposition).
- The Sponsor was to ensure timely delivery of the investigational product. Maintain records for the shipment, receipt, disposition, return and destruction of the investigational product. The Sponsor was to maintain documentation in case the investigational product was retrieved due to expiry or after trial completion.
- The Sponsor was to ensure investigational product stability over the period of use.
- The Sponsor was to provide specifications to the Investigator/ Institution for providing direct access to source data/ documents for trial-related monitoring, audits, IRB/ IEC review, and regulatory inspection. This also included access to written informed consent of subjects, direct access to original medical records, audit, IRB/ IEC review, and regulatory inspection.
- The Sponsor was to evaluate safety data from the trial regularly and inform the Investigator/ Institution and regulatory authority(ies) in case findings affected the safety of subjects in the trial.
- For adverse drug reporting (ADR), the Sponsor was to submit safety reports and periodic reports to the regulatory authority (ies).
- The Sponsor was to evaluate trial conduct and compliance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirements by conduct of audits, as appropriate.
- In case of non-compliance to the protocol, SOPs, GCP and/ or applicable regulatory requirements by the Investigator/ Institution or members of the Sponsor’s staff, the Sponsor was to take prompt action.
- The Sponsor was to ensure that clinical trial study reports were prepared and provided to the regulatory authority (ies).

# 3. INTRODUCTION

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) among young children aged < 5 years. A recent review estimated that RV is accountable for more than 453,000 (420, 000 – 494, 000) deaths per year where the majority of the deaths occur in the developing countries in Asia and Africa [WHO, 2013].

China has the second largest birth cohort in the world and the second highest number of deaths due to RV infection. In China, RV is the most common cause of diarrhoea and an economic burden for the parents. Approximately 27, 000 RV associated deaths occur each year and 32% - 50% of the hospitalised diarrhoea are associated with an RV infection [Naghipour, 2008; Wang, 2009].

In China, introduction of a RV vaccine would most likely be beneficial for children and a significant proportion of the diarrhoeal disease burden might be prevented in the near future [Liu, 2006].

GlaxoSmithKline (GSK) Biologicals has developed an oral live attenuated human rotavirus (HRV) vaccine to meet this health need. GSK Biologicals' lyophilised HRV vaccine has been extensively tested in clinical studies conducted in infants from Europe, North America, Latin America, Asia and Africa. In addition to the lyophilised formulation, GSK Biologicals has also developed a liquid formulation of the human rotavirus (HRV) vaccine. This study evaluated the efficacy, safety and immunogenicity of liquid HRV vaccine in Chinese infants.

## 3.1. Rationale on study design, vaccine administration schedule and indication

### 3.1.1. Rationale for the study

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of a file for licensure in China.

### 3.1.2. Rationale for the study design

This phase III, double-blind, randomised, placebo-controlled, multi-centre study was conducted to assess the efficacy, immunogenicity and safety of GSK Biologicals' liquid HRV vaccine. GSK Biologicals' has already reported the vaccine efficacy and safety in a previous study report dated 29-Oct-2012 and now intends to submit immunogenicity data of the HRV vaccine and co-administered routine vaccines to the China Food and Drug Administration (CFDA). In order to assess the immunogenicity of the HRV vaccine and the co-administered routine vaccines, two immunogenicity sub-cohorts were enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo was assessed in the sub-cohort 1 (N = 600) and the sub-cohort 2 (N=300). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 was assessed in the sub-cohort 2 (N = 300). Reactogenicity of the

liquid HRV vaccine/Placebo was assessed for all the subjects enrolled in the study except for the second immunogenicity sub-cohort and was presented in the previous report.

# 4. STUDY OBJECTIVES (PURPOSE OF THE STUDY)

The study objectives considered for analyses presented in this study report are listed below. Efficacy, reactogenicity and safety objectives were presented in a separate report (ROTA-075) dated 29-Oct-2012.

## 4.1. Secondary objectives

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6.

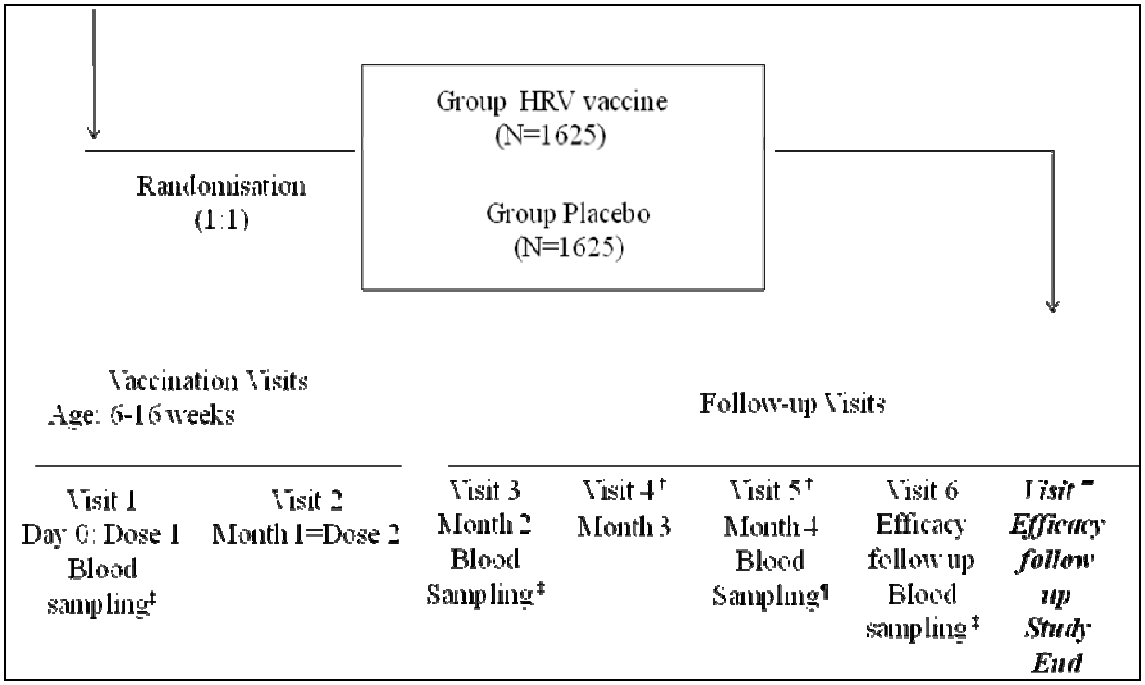
*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

See Section 5.9 for details of the study endpoints.

# 5. INVESTIGATIONAL PLAN

## 5.1. Study design (Overview and description of the protocol)




N: Number of subjects that was planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 was applicable only to subjects in the immunogenicity sub-cohort 2.
‡Blood was drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood was drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 received a dose of OPV at Visit 1, Visit 2 and Visit 3; and received a dose of DTPa at Visit 2, Visit 3 and Visit 4.

### 5.1.1. Overall study design – Description (Discussion of study design)

- Experimental design: Phase III, double-blind, randomised, placebo controlled, multi-centric, single country study with two parallel groups.
- Duration of the study: The subjects were to be followed from study start until approximately April 2012 (i.e. end of RV season in China). The duration of the study, per subject, was planned not to exceed a maximum of 21 months. The study had a single epoch as follows.
  - Primary Epoch: Primary epoch started at Visit 1 (Day 0) and ended at Visit 7 (approximately April 2012 i.e. end of RV season in China).

Table 1 presents the study groups and the epoch in the study.

**Table 1 Study groups and epochs in the study**

| Study group | Planned number of subjects | Age in weeks (MIN/Max) at Dose 1 | Epoch |
|---|---|---|---|
| | | | Primary |
| Group HRV | 1625 | 6 – 16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedules: Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.
  - Subjects in each group were to receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 were to receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study were documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (Planned, N = 1625)
  - Group Placebo (Planned, N = 1625)

The treatment groups for the study are presented in Table 2.

**Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine were given concomitantly with liquid HRV Vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

- Treatment allocation: Randomised with balanced allocation (1:1).
- Blinding**:** Double-blind study.
- Blood Sampling: Blood samples were to be collected from two sub-cohorts of subjects.
  - Immunogenicity sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1 (i.e. Day 0), Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and Visit 6 (i.e. at approximately one year of age).
  - Immunogenicity sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1 (i.e. Day 0), Visit 3 (i.e.

one month post Dose 2 of liquid HRV vaccine/placebo), Visit 5 (i.e. one month post Dose 3 of DTPa) and Visit 6 (i.e. at approximately one year of age).

– Active follow-up for occurrence of GE* episodes was conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

*Note: GE was defined as diarrhoea[#] with or without vomiting.

# Diarrhoea is defined as three or more looser than normal stools per day.

## 5.2. Study procedures

### 5.2.1. Outline of study procedures

Table 3 presents the list of study procedures.

**Table 3 List of study procedures**

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | Visit 7 |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | years 1 of age | April 2012[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | Efficacy follow up |
| Informed consent | ● | | | | | | |
| Re-consenting for Visit 7 follow-up | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | ○ | ○ | ○ | ○ | ○ | ○ |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (~3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (~3mL: sub-cohort 1 and sub-cohort 2) | | ● (~3mL: sub-cohort 2) | ● (~3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+ DTPa) | ● (OPV+ DTPa) | ● (DTPa) | | | |

| **Age** | **6 to 16 weeks** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Epoch** | **Primary** | | | | | **Efficacy follow-up** | |
| **Type of contact** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4 *** | **Visit 5 *** | **Visit 6** | **Visit 7** |
| **Time-points** | **Days 0** | **Months 1** | **Months 2** | **Months 3** | **Months 4** | **years 1 of age** | **April 2012[β]** |
| **Sampling time-points** | **Pre-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Efficacy follow up** | **Efficacy follow up** |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of unsolicited AEs within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | ○ | ○ | ○ | ○ | ○ | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

● used to indicate a study procedure that required documentation in the individual eCRF.
○ used to indicate a study procedure that did not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 were applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
[β]i.e. end of the RV season in China.

### 5.2.2. Intervals between study visits

Table 4 presents the intervals between study visits.

**Table 4 Intervals between study visits**

| Interval | Optimal length of interval[1] | Maximum interval allowed |
|---|---|---|
| 1[2] (Visit 1)→(Visit 2) | 30-48 days | 21-48 days |
| 2[2] (Visit 2)→(Visit 3) | 30-48 days | 21-48 days |
| 3[2] (Visit 3)→(Visit 4) | 30-48 days | 21-48 days |
| 4[2] (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | 1 year of age± 2 weeks[γ] | 1 year of age ± 30 days |
| 6 (Visit 6) → (Visit 7) | 01 April 2012 to 30 April 2012[γ] | 01 April 2012 to 31 May 2012 |

[1]. Whenever possible the investigator arranged study visits within this interval
[2]. Subjects were not eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis of immunogenicity if they made the study visit outside the maximum interval allowed
[γ] It was a defined time point for follow up visit in a range and not an interval.
Note: The date of the previous visit served as the reference date for intervals between study visits.

## 5.3. Selection of study population (Number of cases)

Target enrolment was 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective of efficacy. The estimated rate of non-evaluable subjects was 20%.

There were two sub-cohorts in this study as described below.

- Immunogenicity Sub-cohort 1 (N=600)
- Immunogenicity Sub-cohort 2 (N=300).

Subjects in each group received routine childhood vaccinations according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 received DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose.

### 5.3.1. Inclusion criteria for enrolment (Selection of subjects)

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

- Subjects who the investigator believed that their parents/Legally Acceptable Representatives (LARs) could and would comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent/LARs of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.

- Born after a gestation period of 36 to 42 weeks inclusive.

### 5.3.2. Exclusion criteria (Selection of subjects)

The following criteria were checked at the time of study entry. If **ANY** exclusion criterion was applicable, the subject was not included in the study:

- Child in care.

  Refer to the GLOSSARY OF TERMS for the definition of child in care.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone ≥ 0.5 mg/kg/day, or equivalent, inhaled and topical steroids were allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccines and ending 14 days after the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or would be exposed to an investigational or a non-investigational product (pharmaceutical product or device).
- Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for Intussusception (IS).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness.
- History of confirmed RV GE.
- Acute disease and/or fever at the time of enrolment.
  - Fever was defined as temperature ≥37.1°C on axillary setting as defined by the Chinese authorities.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).

- GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

In addition to the criteria mentioned above, the following criteria were applicable to all subjects in the immunogenicity sub-cohort 2:

- History of diphtheria, tetanus and pertussis disease.
- History of seizures or progressive neurological disease.
- Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

### 5.3.3. Elimination criteria

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

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this meant prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and 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 the liquid HRV vaccine/placebo and ending 14 days after, with the exception of routine childhood vaccinations.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition likely to alter the immune response or are confirmed to have an immunodeficiency condition.

### 5.3.4. Subject completion and withdrawal

#### 5.3.4.1. Subject completion

A subject who returned for the concluding visit in the protocol was considered to have completed the study.

#### 5.3.4.2. Subject withdrawal

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

Withdrawals were not replaced.

##### *5.3.4.2.1. Subject withdrawal from the study*

From an analysis perspective, a 'withdrawal' from the study referred to any subject who did not come back for the concluding visit foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject was used for the analysis.

A subject was considered 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 documented in the eCRF. The investigator documented whether the decision to withdraw a subject from the study was made by the subject's parents/ LARs, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

##### *5.3.4.2.2. Subject withdrawal from investigational vaccine*

A 'withdrawal' from the investigational vaccine referred to 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 vaccine was not necessarily withdrawn from the study as further study procedures or follow-up could be performed (safety or immunogenicity) as planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine was documented on the Vaccine Administration screen of the eCRF. The investigator documented whether the decision to discontinue further vaccination/treatment was made by the subject's parents/ LARs or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-SAE.
- Other

## 5.4. Composition and administration of vaccine (Investigational Products

### 5.4.1. Description of vaccines

Table 5 presents the formulation and presentation of study vaccines.

**Table 5 Study vaccines**

| Name of the Investigational Products: | liquid HRV vaccine | Placebo | DTPa | OPV |
|---|---|---|---|---|
| **Dosage form:** | Refer to Section 5.4.2 | Refer to Section 5.4.2 | Refer to Section 5.4.2 | Refer to Section 5.4.2 |
| **Source:** | RIX4414 HRV strain at least $10^{6.0}$ median $CCID_{50}$, Di-sodium Adipate 132.74 mg, DMEM 2.26 mg, Sucrose 55% (w/w), water for injection q.s. as 1.5 mL. | Di-sodium Adipate 132.74 mg, DMEM 2.26 mg, Sucrose 55% (w/w), water for injection q.s. as 1.5 mL. | Diphtheria toxoid ≥ 30 international units (IU) 25 Limits of flocculation (Lf),Tetanus toxoid ≥ 40 IU (10Lf), Pertussis toxoid 25 µg, Filamentous haemagglutinin 25 µg, Pertactin 8 µg, Aluminium as salts 0.5 mg, 2-phenoxyethanol ≤ 2.5 mg. | per 0.1ml(2 drops) Total polio-virus, not less than 6.15$lgCCID_{50}$ type1, not less than 6.0 $lgCCID_{50}$ type2, not less than 5.0 $lgCCID_{50}$ type3, not less than 5.5 $lgCCID_{50}$ |
| **Lot number (Batch Number)** | AROLA219B | PROLA008A | YC14B113AA | [20100202] |
| **Presentation (Specification)** | Liquid in a pre-filled oral applicator | Liquid in a pre-filled oral applicator | Turbid white suspension in a pre-filled syringe | liquid, oral |
| **Expiry date(Valid period)** | 30 September, 2012 | 31 October 2012 | 01 July,2012 | 01 February,2012 |

**Storage conditions:** Study vaccines were stored at the defined temperature range (i.e. +2 to +8°C).

The liquid HRV vaccine and placebo used in this study were developed and manufactured by GSK Biologicals.

The DTPa vaccine used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 was developed and manufactured by GSK Biologicals.

The OPV vaccine used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 was developed and manufactured by Institute of Medical Biology, Chinese Academy of Medical Sciences.

The Quality Control Standards and Requirements for the liquid HRV vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals were obtained.

The vaccines were labelled and packed according to applicable regulatory requirements.

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

### 5.4.2. Dosage and administration including administration route and basis for determining the administration route of study vaccines

The pre-filled oral applicator was shaken well before use. The product [HRV vaccine or placebo] was then administered smoothly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration occurred in a quiet environment. Sufficient time was allowed for the baby to swallow the liquid vaccine solution, to avoid regurgitation or vomiting. If the subject regurgitated or vomited after study vaccine administration, no new study vaccine dose was administered. The subject continued to participate in the study. The oral vaccine intake characteristics (smooth vaccine intake, vaccine intake interrupted due to coughing or choking, regurgitation after vaccine intake, vomiting after vaccine intake) were recorded in the eCRF.

The vaccination regimen is summarised in Table 6.

**Table 6 Dosage and administration**

| Type of contact and time-point | Doses | Treatment Group | Vaccine | Route [1] | Site [2] | Side [3] |
|---|---|---|---|---|---|---|
| Visit 1 (day 0); Visit 2 (month 1) | 1 | Group HRV vaccine | liquid HRV vaccine | O | | |
| Visit 1 (day 0); Visit 2 (month 1) | 1 | Group Placebo | Placebo | O | | |
| Visit 2 (month 1); Visit 3 (month 2); Visit 4 (month 3) | 1 | Group HRV vaccine<br>Group Placebo (sub-cohort 2) | DTPa | IM | Ant T | L |
| Visit 1 (day 0); Visit 2 (month 1); Visit 3 (month 2) | 1 | Group HRV vaccine<br>Group Placebo (sub-cohort 2) | OPV | O | | |

[1]Oral (O)/ Intramuscular (IM)
[2]Thigh (T): Anterolateral (Ant)
[3]Left (L)

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

### 5.4.3. Contraindications to subsequent vaccination

***GSK Biologicals' liquid HRV vaccine or placebo:***

The following events constituted absolute contraindications to further administration of the liquid HRV vaccine or placebo. If any of these events occurred during the study, the subject did not receive additional doses of the vaccine but continued other study procedures at the discretion of the investigator.

- Hypersensitivity reaction following the administration of the liquid HRV vaccine or placebo.
- Intussusception (IS) and any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following events constituted contraindications to administration of liquid HRV vaccine and placebo at that point in time; if any of these events occurred at the time scheduled for vaccination, the subject was vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator.

- Acute disease at the time of vaccination. Acute disease was defined as the presence of a moderate or severe illness with or without fever. (Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.) All vaccines could be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness.
- GE within 7 days preceding the study vaccine administration.

***GSK Biologicals' DTPa vaccine:***

- DTPa vaccine was not administered to subjects with known hypersensitivity to any component of the vaccine or to subjects who showed signs of hypersensitivity after previous administration of DTPa vaccine.
- DTPa vaccine was contra-indicated if the child had experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances the vaccination course was continued with diphtheria and tetanus vaccine.

### 5.4.4. Warnings and precautions

*Warnings and precautions related to the liquid HRV vaccine*

The liquid HRV vaccine was under no circumstances to be injected.

*Warnings and precautions related to the DTPa*

It is a good clinical practice that immunisation is preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of DTPa vaccine was to be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, was not a contra-indication.

If any of the following events occurred in temporal relation to receipt of DTPa, the decision to give subsequent doses of vaccine containing the pertussis component was carefully considered. There may have been circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events were not associated with permanent sequelae.

The following events were previously considered contra-indications for Diphtheria Tetanus whole cell Pertussis (DTPw) and are now considered general precautions:

  - Temperature of ≥ 40.5°C within 48 hours of vaccination, not due to another identifiable cause.
  - Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
  - Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
  - Convulsions with or without fever, occurring within 3 days of vaccination.

- In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it was better to defer pertussis (Pa) immunisation until the condition was corrected or stable. However, the decision to give pertussis vaccine was to be made on an individual basis after careful consideration of the risks and benefits.
- A history of febrile convulsions and a family history of convulsive fits did not constitute contra-indications.
- HIV infection was not considered as a contra-indication.
- As with all injectable vaccines, appropriate medical treatment was readily available in case of anaphylactic reactions followed by the administration of the vaccine. For this reason, the vaccinee remained under medical supervision for 30 minutes after immunisation.
- As for all diphtheria, tetanus and pertussis vaccines, the vaccine was to be given deep intramuscularly and preferably at alternate injection sites.
- DTPa vaccine was to be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding could occur following an intramuscular administration to these subjects.

- DTPa vaccine was under no circumstances administered intravenously.
- The potential risk of apnoea and the need for respiratory monitoring for 48-72h was to be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination was high in this group of infants, vaccination was not withheld or delayed.

For warnings and precautions related to the OPV vaccines, please refer to the respective product labels/package inserts.

## 5.4.5. Treatment allocation and randomisation

The treatment allocation at the investigator site was performed using SBIR. The treatment numbers were allocated by kit. The randomisation algorithm used a minimisation procedure accounting for centre.

When SBIR was not available, the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions was used for reference.

After the eligibility of the subject was checked and ICF obtained, the site staff in charge of the vaccination accessed SBIR. Upon providing the subject identification number, the randomisation system used the minimisation algorithm to determine the treatment number to be used for the subject. Each treatment number was recorded in the eCRF on the Vaccine Administration screen.

### 5.4.5.1. Randomisation of supplies

The randomisation was performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, a 6% over-randomisation of supplies was prepared.

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

## 5.4.6. Randomisation of subjects to assay sub-cohorts

Randomisation for all the sub-cohorts was done in parallel. Blood samples were collected from both the sub-cohorts of subjects:

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).
- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300).

## 5.5. Blinding

The study was conducted in a double-blind manner with respect to the liquid HRV vaccine and placebo. The parents/LARs of the subjects, the study personnel and the investigator were unaware of the study vaccine administered (liquid HRV vaccine/Placebo).

The protocol stated that the level of the blinding was to be maintained throughout the conduct of the trial and that appropriate personnel was only to be unblinded when data was cleaned to an acceptable level of quality or when required in case of an SAE. However, the study data was accidentally unblinded to the study team members involved in managing data at the time of data transfer. The unblinded information was not shared with any study team members involved in analysis and interpretation. The communication relevant to this incident was deleted to maintain the integrity of the analysis.

The final analysis was done by GSK.

## 5.6. Prior and concomitant medication /vaccinations

At each study visit, the investigator questioned the subject's parents/LARs about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, were recorded in the eCRF. This also applied to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

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 was considered to be prophylactic when it was given in the absence of fever and any other symptom, to prevent fever from occurring [Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities].

Similarly, concomitant medication administered for the treatment of a SAE, at any time, was recorded on the SAE screens in the eCRF.

## 5.7. Laboratory assays and time-points (Observational index and observational list for Laboratory testing)

Two aliquots were prepared for all serological samples: One aliquot was to be shipped to the National Institutes for Food and Drug Control (NIFDC) in China. NIFDC performed all serological assays using standardised and validated procedures. The other aliquot was to be transferred to GSK Biologicals designated laboratory for back-up.

Serum anti-rotavirus IgA antibody concentrations were to be measured in all serum samples collected at Visit 1, Visit 3 and Visit 6 using ELISA. The assay cut-off was 20 U/mL. Antibodies to all antigens contained in the co-administered vaccines were to be

measured at Visit 1 and Visit 5 (applicable only for subjects in the immunogenicity sub-cohort 2).

The laboratory assays to be performed are presented in Table 7.

**Table 7 Laboratory Assays**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | NIFDC |
| Serum | anti-diphtheria | ELISA | NIFDC | IU/mL | 0.1 | NIFDC |
| Serum | anti-tetanus | ELISA | NIFDC | IU/mL | 0.1 | NIFDC |
| Serum | anti-PT | ELISA | NIFDC | EL.U/mL | 5 | NIFDC |
| Serum | anti-FHA | ELISA | NIFDC | EL.U/mL | 5 | NIFDC |
| Serum | anti-PRN | ELISA | NIFDC | EL.U/mL | 5 | NIFDC |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | NIFDC |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | NIFDC |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | NIFDC |

ELISA = Enzyme Linked Immunosorbent Assay
NIFDC = National Institute for Food and Drug Control
U = Units; IU = International Units; EL.U = Elisa Units
†ED50 = Estimated dose 50% is the seroprotective level.

Collected samples were used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

## 5.8. Assessment of immunogenicity variables (Observational index and observational list for Laboratory testing)

Table 8 presents the summary of blood sampling time-points and assays for the assessment of immunology variables.

**Table 8 Summary of blood sampling time-points and assays for the assessment of immunology variables**

| Blood sampling time-point | | Sub-cohort Name | No.of subjects | Component | Components priority rank |
|---|---|---|---|---|---|
| Type of contact and time-point | Sampling time-point | | | | |
| Visit 1 (day 0) | Pre-Vacc | Immunogenicity Sub-cohort 1 | 600 | anti-RV IgA antibody | None |
| Visit 1 ( day 0) | Pre-Vacc | Immunogenicity Sub-cohort 2 | 300 | anti-RV IgA antibody, Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | anti-RV IgA antibody, Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 3 (month 2) | Post-Vacc § | Immunogenicity Sub-cohort 1 | 600 | anti-RV IgA antibody | None |
| Visit 3 (month 2) | Post-Vacc § | Immunogenicity Sub-cohort 2 | 300 | anti-RV IgA antibody | None |
| Visit 5 (month 4) | Post-Vacc * | Immunogenicity Sub-cohort 2 | 300 | Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN |
| Visit 6 (approximately one year of age) | Efficacy follow up | Immunogenicity Sub-cohort 1 | 600 | anti-RV IgA antibody | None |
| Visit 6 (approximately one year of age) | Efficacy follow up | Immunogenicity Sub-cohort 2 | 300 | anti-RV IgA antibody | None |
| **GE stool analysis** | | | | | |
| Visit 1 (Days 0) to Visit 7 (April 2012)[β] | Throughout the study period | All subjects | | RV antigen | None |

D = Diphtheria, T = Tetanus

§ Post-Vacc 2: One month post Dose 2 of liquid HRV vaccine/placebo

*Post-Vacc 3: Two month post Dose 3 of OPV and one month post of Dose 3 of DTPa

[β] i.e. end of RV season in China.

### 5.8.1. Immunological correlates of protection

No immunological correlate of protection has been demonstrated so far for the anti-RV IgA antibody.

Antibodies against the pertussis components PT, FHA and PRN were measured by an ELISA technique developed by National Institutes for Food and Drug Control (NIFDC). ELISA antigens, standard sera for diphtheria and tetanus assays, positive and negative control sera for rotavirus ELISA were provided by GSK Biologicals'. For the pertussis antigens the cut-off of the test was set at 5 ELISA units per ml (EL.U/ml). As per

Chinese regulatory requirements, the clinical cut-off (vaccine response) for anti-PT and anti-FHA was defined at ≥20 EL.U/ml. The response to PRN is evaluated via the calculation of at least a 4-fold increase in antibody concentrations from pre to post-vaccination. No serological correlate of protection against pertussis has been established [Granström, 1987; Karpinsky, 1987]. Therefore seropositivity and vaccine response rates are used to evaluate vaccine immunogenicity. Subjects with antibody concentration for PT, FHA and PRN below the cut-off of 5 EL.U/ml are considered seronegative.

Specific antibodies against diphtheria toxoid (anti-diphtheria) and tetanus toxoid (anti-tetanus) were measured by ELISA. The assay cut-off of the tests was set at 0.1 IU/ml, which provides a conservative estimate of the percentage of subjects deemed to be protected [Camargo, 1984; Melville-Smith, 1983].

Antibodies against poliovirus types 1, 2 and 3 were determined by a virus micro-neutralization test adapted from the World Health Organization Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis [WHO, 1993]. The lowest dilution at which serum samples were tested was 1:8, from which a test was considered positive. Titers were expressed in terms of the reciprocal of the dilution resulting in 50% inhibition. Antibody titers greater than or equal to this value are considered as protective.

## 5.9. Statistical methods (Statistical Processing Scheme)

The statistical analyses were performed using the SDD (i.e **S**AS **D**rug and **D**evelopment) web portal version 3.5.

The study endpoints considered for analyses presented in this study report are listed below. Methodology and results for efficacy, reactogenicty and safety objectives were presented in a separate report (ROTA-075) dated 29-Oct-2013.

### 5.9.1. Secondary Outcome/Efficacy Variables

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and at Visit 6.

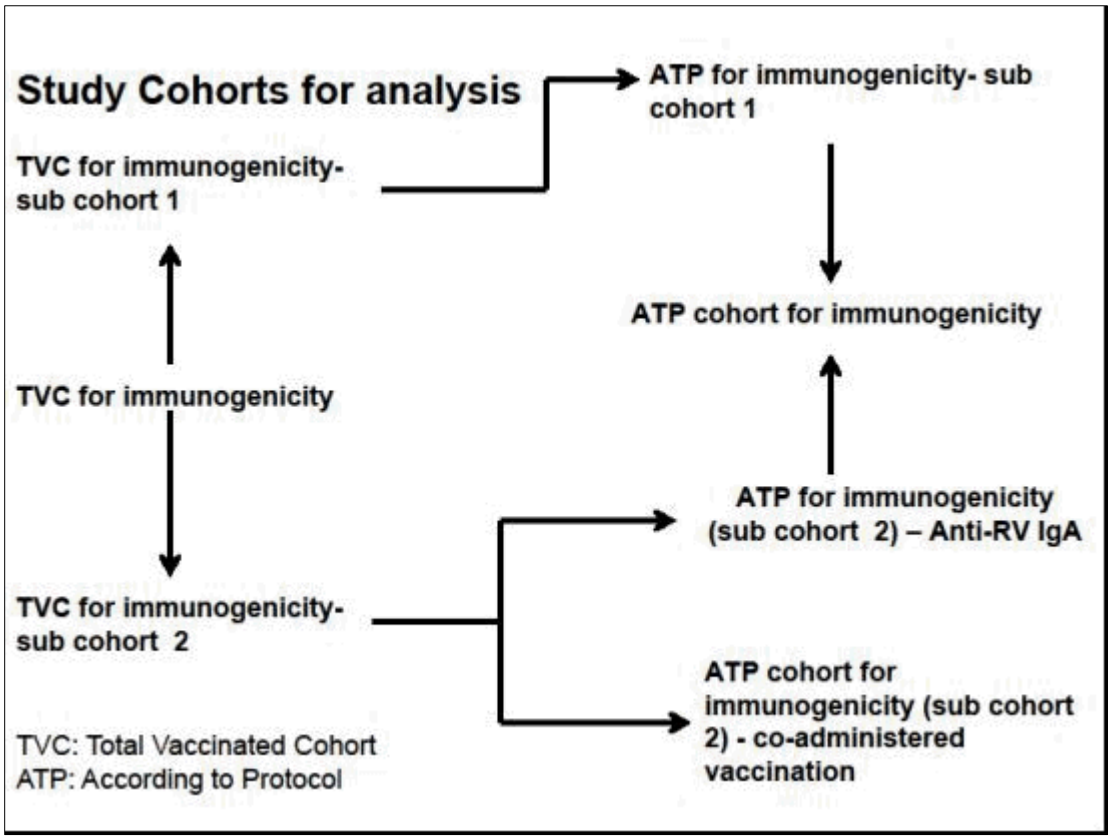
*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as GMCs at Visit 3 and at Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  - Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

### 5.9.2. Determination of sample size

Target enrolment was to enrol 3250 eligible subjects (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group) for the evaluation of efficacy (primary objective). Out of 3250 subjects, 900 subjects were enrolled into the immunogenicity sub cohorts (600 subjects in the immunogenicity sub cohort 1and 300 subjects in the immunogenicity sub cohort 2) according to 1:1 randomization ratio.

### 5.9.3. Study cohorts /data sets analyzed



#### 5.9.3.1. Total vaccinated cohort

The total vaccinated cohort included all subjects with at least one dose of the liquid HRV vaccine or placebo administration documented:

- The immunogenicity analysis based on the total vaccinated cohort included all vaccinated subjects from the immunogenicity sub-cohorts for whom immunogenicity data are available.

#### 5.9.3.2. ATP cohort for analysis of safety

The ATP cohort for safety included all vaccinated subjects:

- who received at least one dose of HRV vaccine/Placebo according to their random assignment.
- for whom the randomisation code was not broken, who did not received a vaccine forbidden by or not specified in the protocol.

#### 5.9.3.3. ATP cohort for analysis of efficacy

The ATP cohort for efficacy included all subjects from the ATP cohort for safety.

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

#### 5.9.3.4. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity included subjects in the immunogenicity sub-cohorts from the ATP cohort for safety (refer to section 5.9.3):

- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol up to Visit 3,
- with no protocol violation of demographics (unknown age at study entry or outside the protocol defined age interval),
- who complied with vaccination schedule of liquid HRV vaccine or placebo,
- who complied with blood sampling schedule till Visit 3,
- for whom immunogenicity data was available, at pre and post sampling time-points (at Visit 3),

- who did not have concomitant infection unrelated to the vaccine up to Visit 3, which could influence the immune response,
- who did not have RV other than vaccine strain in GE stool samples collected up to Visit 3,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1.

For the analysis of anti-RV IgA antibody (sub-cohort 2) the cohort was called, ATP cohort for immunogenicity (sub-cohort 2) – anti-RV IgA antibody.

For the analysis of co-administered vaccines (sub-cohort 2) along with points 1, 2, 3, & 7 the below mentioned criteria was also considered. This is the "ATP cohort for immunogenicity (sub-cohort 2) – co-administered vaccination".

- who had complete vaccination for OPV & DTPa (all three doses received).
- who complied with vaccination schedule for the co-administered vaccines.
- who complied with blood sampling schedule for the analysis of co-administered vaccines (Visit 5).
- for whom immunogenicity data was available, at post sampling time-point (Visit 5).

The ATP cohort for immunogenicity was used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort was planned to be performed only if more than 5% of the vaccinated subjects with available results were excluded from the ATP cohort for immunogenicity. In such a case, the total vaccinated cohort analyses would evaluate whether exclusion from the ATP cohort could have biased the results.

### 5.9.4. Derived and transformed data

- A seronegative subject was a subject whose antibody concentration/titre was below the assay cut-off.
- A seropositive subject was a subject whose antibody concentration was equal or above the cut-off value. The following seropositivity thresholds were applicable:
  - Anti-PT, Anti-PRN and anti-FHA antibody concentrations ≥ 5 El.U/ml
  - Anti rotavirus IgA antibody concentration ≥ 20 U/mL
- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds were applicable:
  - Anti-diphtheria antibody concentration ≥ 0.1 IU/ml
  - Anti-tetanus antibody concentration ≥ 0.1 IU/ml
  - Anti-poliovirus types 1, 2 and 3 antibody titre ≥ 8.

- Vaccine response to the pertussis antigens was defined as:
  - For PT and FHA, response was defined as an antibody concentration ≥ 20 EL.U/ml at post-vaccination.
  - For PRN, response was defined as post-vaccination antibody concentration ≥ 20 EL.U/ml (4-fold the assay cut-off) for initially seronegative subjects and at least a 4-fold increase in antibody concentration from pre to post-vaccination for initially seropositive subjects.
- Seroconversion is defined as the appearance of anti-RV IgA antibodies (i.e. concentration greater than or equal to the cut-off value) in the serum of subjects who were seronegative before vaccination.
- The Geometric Mean Concentration (GMC) calculations were performed by taking the anti-log of the mean of the $\log_{10}$ antibody concentrations 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 the immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

### 5.9.5. Analysis of demographics (Analysis)

**Demography**

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

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 was calculated per group and overall. The racial and gender composition were presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and over all. The distribution of subjects enrolled among the study centres was tabulated as a whole and per group. The percentages of subjects who received concomitant and intercurrent vaccinations were tabulated by group.

### 5.9.6. Analysis of immunogenicity (Analysis)

The primary analysis was based on the ATP cohort for the analysis of immunogenicity. As the percentage of enrolled subjects excluded from this ATP cohort was more than 5%, a secondary analysis based on the Total Vaccinated cohort was performed to complement the ATP analysis.

**For subjects in the immunogenicity sub-cohort 2:**

For each treatment group, anti-D, anti-T, anti-PT, anti-FHA, anti-PRN and anti-poliovirus serotype 1, 2 and 3 antibodies at pre-vaccination and at Visit 5 was summarized as follows:

- Seroprotection /seropositivity rates and their exact 95% CIs was calculated [Clopper, 1934].
- GMT/GMCs and their 95% CIs were calculated.
- The distribution of antibody concentrations at post-vaccination time point for each antigen was displayed using the reverse cumulative curves (RCCs).

**For each sub-cohort 1 and sub-cohort 2 and the pooled sub-cohort:**

For each treatment group, anti-rotavirus IgA antibodies measured at pre-vaccination & at post-vaccination were summarized as follows:

- Seroconversion/seropositivity rates and their exact 95% CI were calculated [Clopper, 1934].
- GMCs and their 95% CI were calculated.
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the Placebo group were computed [Newcombe, 1998].
- The asymptotic standardised 95% CI for difference in the percentage of subjects who are seropositive for anti-rotavirus IgA antibody concentrations at Visit 6 between the HRV vaccine and the Placebo group were computed [Newcombe, 1998].
- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 was displayed using reverse cumulative curves (RCCs).

An exploratory analysis of immunogenicity for anti-rotavirus IgA antibody was performed by excluding the subjects who took anti viral drugs from dose 1 to Visit 3.

An exploratory analysis summarizing the anti-rotavirus IgA seropositivity status and GMCs at Visit 6 by excluding the subjects reporting RVGE from Dose 1 up to Visit 6 was performed.

### 5.9.7. Analysis of efficacy

- An exploratory/supportive analysis of vaccine efficacy by serostatus of subjects against rotavirus IgA antibody at Visit 3 was performed on ATP cohort for efficacy**.** A similar analysis was performed considering the serostatus at Visit 6 for the efficacy data collected from Visit 6 up to Visit 7 on ATP cohort for efficacy for second year follow up.

### 5.9.8. Sequence of analyses

At study conclusion, the final analysis of efficacy, reactogenicity and safety was done and the data was presented in an earlier clinical study report (CSR). for the study. The immunogenicity data was not available at that time and the current annex CSR aims to present this data.

### 5.9.9. Interim analysis

No interim analysis was planned for this study.

## 5.10. Data quality assurance at study level

To ensure that the study procedures conformed across all investigator sites, the protocol, electronic 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. An investigator meeting was held prior to the study start.

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

During the course of the study, the following issues with regard to the conduct of the study were identified, either via site monitoring activities or were brought to GSK Biologicals' attention by other oversight mechanisms. These issues were investigated and corrective and / preventive actions where possible were taken as described below.

The serology data was accidently unblinded to the study team members involved in managing data at the time of data transfer, but was not shared with any study team members involved in analysis and interpretation. The communication relevant to this incident was deleted to maintain integrity of the analysis.

No subject was eliminated because of this deviation.

**Independent Audit statement:**

- This study was subject to audit by GSK's Clinical Development Quality Assurance (CDQA) at the centre number [redacted] on 26th-27th June 2010.

## 5.11. Changes in the conduct of the study or planned analyses (Modification in process of study)

### 5.11.1. Protocol amendments

**Protocol Amendment 1 (02 September 2010):**

The following changes were reflected in Protocol amendment 1: Over-randomisation of supplies would be 6%, parallel randomisation of subjects to assay sub-cohorts and change in time periods for administration of medications/products that could have led to the elimination of a subject from ATP analyses.

**Protocol Amendment 2 (05 August 2011):**

The protocol was amended again on 05 August 2011 to reflect the extension of the efficacy follow-up period until the end of the second RV season in China. Based on the preliminary review of GE episodes reported prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seemed lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up was extended until approximately April 2012 (i.e. end of RV season in China).

### 5.11.2. Other changes

This study was conducted according to the protocol.

Analyses were performed as planned in the protocol and/or SAP except for the following changes:

- The “according to protocol cohort” used for the analysis of the antigens in the co-administered vaccines was changed from “ATP cohort for immunogenicity– co-administered vaccination” to “ATP cohort of immunogenicity (sub cohort 2) – co-administered vaccination”
- The cohort used for the analysis of anti-RV IgA in immunogenicity sub cohort 2 was changed to “ATP cohort for Immunogenicity (sub cohort 2) – anti-RV IgA” to differentiate between the cohorts used for analysis of co-administered vaccines and the analysis of anti-RV IgA.
- An analysis on the pooled immunogenicity sub cohort 1 and sub cohort 2 was also performed for anti-RV IgA antibodies.

# 6. STUDY POPULATION RESULTS (STUDY RESULTS)

## 6.1. Study dates

The first subject was enrolled in the study on 29 August 2010 and the last study visit was on 12 May 2012.

## 6.2. Subject eligibility and attrition from the study

### 6.2.1. Number of subjects

The number of subjects enrolled in the study by centre is presented in the following table:



### 6.2.2. Protocol deviations at subject level

#### 6.2.2.1. Protocol Deviations leading to elimination from ATP analyses

The deviations are presented in the following tables:

#### 6.2.2.2. Protocol Deviations not leading to elimination from ATP analyses

Protocol deviations not leading to elimination from ATP analyses have been presented in the report dated 29-OCT-2012.

## 6.3. Demographic characteristics

### 6.3.1. ATP cohort for immunogenicity

The demographic characteristics are presented in the following table:



### 6.3.2. Total Vaccinated cohort

The demographic characteristics are presented in the following table:



# 7. IMMUNOGENICITY RESULTS

## 7.1. Data sets analyzed

The analysis of immunogenicity was performed on the ATP cohort for immunogenicity. Since more than 5% of the subjects were eliminated from the ATP cohort for immunogenicity, a secondary analyses on the Total Vaccinated cohort with available results was performed. See Section 5.9.3 for the definition of the cohorts identified for analyses.

## 7.2. According-to-protocol analysis

### 7.2.1. Anti-rotavirus IgA antibody response

The results are detailed in the following table and figures:

**Immunogenicity sub cohort 1:** Immunogenicity of liquid HRV vaccine.

***Visit 3 (Month 2)***

- Anti-rotavirus IgA seroconversion rate was 74.7% [95% CI: 68.9%; 79.9%] in the HRV group one month post-Dose 2 of HRV vaccination. Anti-rotavirus IgA seropositivity rate was 3.5% [95% CI: 1.6%; 6.6%] in the Placebo group one month post-Dose 2 of placebo (Table 24).

- Anti-rotavirus IgA antibody GMCs in overall subjects were 90.2 U/ml [95% CI: 73.3; 111.1] in the HRV group and < 20 U/ml in the placebo group one month post-Dose 2 of HRV vaccine/placebo (Table 24).

***Visit 6 (Month 12)***

- Anti-rotavirus IgA antibody seropositivity rate was 71.5% [95% CI: 65.5%; 77.1%] in the HRV group at approximately one year of age. Anti-rotavirus IgA seropositivity rate was 46.8% [95% CI: 40.5%; 53.2%] in the Placebo group at approximately one year of age (Table 24).
- Anti-rotavirus IgA antibody GMCs in overall subjects were 66.5 U/ml [95% CI: 54.6; 81.0] in the HRV group and 35.3 U/ml [95% CI: 29.3; 42.5] in the placebo group at approximately one year of age (Table 24).

**Immunogenicity sub cohort 2:** Immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines.

***Visit 3 (Month 2)***

- Anti-rotavirus IgA antibody seroconversion rate was 64.2% (95% CI: 55.4%; 72.3%) in the HRV group, one month post-Dose 2 of HRV vaccine. Anti-rotavirus IgA seropositivity rate was 9.4% (95% CI: 5.1%; 15.5%) in the Placebo group, one month post-Dose 2 of placebo (Table 24).
- Anti-rotavirus IgA antibody GMCs in overall subjects was 84.0 U/ml [95% CI: 58.9; 119.8] in the HRV group and < 20 U/ml in the placebo group, at one month post-Dose 2 of HRV vaccine/placebo (Table 24).

***Visit 6 (Month 12)***

- Anti-rotavirus IgA antibody seropositivity rate was 50.0% (95% CI: 40.9%; 59.1%) in the HRV group, at approximately one year of age. Anti-rotavirus IgA seropositivity rate was 21.8% (95% CI: 15.1%; 29.8%) in the Placebo group, at approximately one year of age (Table 24).
- Anti-rotavirus IgA antibody GMCs in overall subjects was 31.3 U/ml [95% CI: 24.6; 39.8] observed in the HRV group and <20 U/ml in the placebo group, at approximately 1 year of age (Table 24).

### 7.2.2. Antibody response to diphtheria toxoid and tetanus toxoid

The results are detailed in the following table and figures:

Table 31 Anti-Diphtheria and anti-Tetanus antibody GMC and seroprotection rates at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 7 Reverse cumulative curves for anti-diphtheria antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 8 Reverse cumulative curves for anti-tetanus antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

- The anti-diphtheria and anti-tetanus antibody seroprotection rates (defined as antibody concentrations ≥ 0.1 IU/ml) at one month post-Dose 3 of DTPa vaccine was 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group (Table 31).
- At one month post-dose 3 of DTPa vaccine, the anti-diphtheria antibody GMCs reported for the HRV group was 0.375 IU/ml [95% CI: 0.326; 0.432] and for the Placebo group was 0.334 IU/ml [95% CI: 0.308; 0.363]. (Table 31).
- At one month post-dose 3 of DTPa vaccine, the anti-tetanus antibody GMCs reported for the HRV group was 1.281 IU/ml [95% CI: 1.253; 1.309] and for the Placebo group was 1.343 IU/ml [95% CI: 1.215; 1.486] (Table 31).

### 7.2.3. Antibody response to PT, FHA and PRN

The results are detailed in the following table and figures:

Table 32 Anti-PT, anti-FHA and anti-PRN antibody GMC and seropositivity rates at one month post dose 3 of DTPa of vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Table 33 Vaccine response for anti-PT and anti-FHA antibodies at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Table 34 Vaccine response for Anti-PRN antibody at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 12 Reverse cumulative curves for anti-FHA antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 13 Reverse cumulative curves for anti-PT antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 14 Reverse cumulative curves for anti PRN concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

- The anti-PT, anti-FHA, and anti-PRN antibody seropositivity rates (defined as antibody concentrations ≥ 5 EL.U/ml) were 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, at one month post-Dose 3 of DTPa vaccine (Table 32).

- At one month post-dose 3 of DTPa vaccine, the anti-PT antibody GMCs reported for the HRV group was 88.9 U/ml [95% CI: 84.9; 93.2] and for the Placebo group was 90.5 U/ml [95% CI: 86.4; 94.8] (Table 32).
- At one month post-dose 3 of DTPa vaccine, the anti-FHA antibody GMCs reported for the HRV group was 59.5 U/ml [95% CI: 55.8; 63.5] and for the Placebo group was 65.8 U/ml [95% CI: 61.3; 70.5] (Table 32).
- At one month post-dose 3 of DTPa vaccine, the anti-PRN antibody GMCs reported for the HRV group was 41.9 U/ml [95% CI: 37.6; 46.5] and for the Placebo group was 50.8 U/ml [95% CI: 44.3; 58.1] (Table 32).

### 7.2.4. Antibody response to poliovirus types 1, 2 and 3

The results are detailed in the following table and figures:

Table 35 Anti-Poliovirus 1, 2 and 3 antibody GMT and seroprotection rates at two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 9 Reverse cumulative curves for anti-polio 1 antibody titres at two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 10 Reverse cumulative curves for anti-polio 2 antibody titres two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

Figure 11 Reverse cumulative curves for anti-polio 3 antibody titres two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

- Anti-poliovirus type 1 and 2 antibody seroprotection rates (defined as antibody titres $\geq 8$ $ED_{50}$) were 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, two months post-Dose 3 of OPV vaccine (Table 35).
- Anti-poliovirus type 3 antibody seroprotection rate (defined as antibody titres $\geq 8$ $ED_{50}$) was 99.3% [95% CI: 96.0%; 100%] in the HRV group and 99.3% [95% CI: 96.1%; 100%] in the placebo group, two months post-Dose 3 of OPV vaccine (Table 35).
- At two months post-dose 3 of OPV vaccine, the anti-Polio 1 antibody GMTs reported for the HRV group was 2101.1 [95% CI: 1734.8; 2544.8] and for the Placebo group was 2259.4 [95% CI: 1844.4; 2767.9] (Table 35).
- At two months post-dose 3 of OPV vaccine, the anti-Polio 2 antibody GMTs reported for the HRV group was 402.5 [95% CI: 334.8; 483.9] and for the Placebo group was 425.1 [95% CI: 371.0; 487.1] (Table 35).

- At two months post-dose 3 of OPV vaccine, the anti-Polio 3 antibody GMTs reported for the HRV group was 426.6 [95% CI: 342.7; 531.0] and for the Placebo group was 360.3 [95% CI: 303.0; 428.3] (Table 35).

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

The results are detailed in the following table and figures:

Table 36 Number and percentage of subjects reporting RVGE cases during the period between Visit 3 and Visit 6 classified by their anti-rotavirus IgA status at Visit 3 and Visit 6 (ATP cohort for efficacy)

Table 37 Number and percentage of subjects reporting severe RVGE cases during the period between Visit 3 and Visit 6 classified by their anti-rotavirus IgA status at Visit 3 and Visit 6 (ATP cohort for efficacy)

Table 38 Number and percentage of subjects reporting RVGE cases from Visit 6 up to Visit 7 classified by their anti-rotavirus IgA status at Visit 6 (ATP cohort for efficacy for second year)

Table 39 Number and percentage of subjects reporting severe RVGE cases from Visit 6 up to Visit 7 classified by their anti-rotavirus IgA status at Visit 6 (ATP cohort for efficacy for second year)

Table 40 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

Table 41 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

Table 42 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

Table 43 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

Table 44 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from Visit 6 to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 6 (ATP cohort for efficacy for second year follow up)

Table 45 Percentage of subjects reporting severe RV GE episode and efficacy of the vaccine from Visit 6 to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 6 (ATP cohort for efficacy for second year)

## 7.3. Total vaccinated cohort analysis

### 7.3.1. Anti-rotavirus IgA antibody response

The results are detailed in the following table and figures:

### 7.3.2. Antibody response to diphtheria toxoid and tetanus toxoid

The results are detailed in the following table and figures:

Table 53 Anti-Diphtheria and anti-Tetanus antibody GMC and seroprotection rates at one month post dose 3 of DTPa vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

Figure 21 Reverse cumulative curves for anti-diphtheria antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)

Figure 22 Reverse cumulative curves for anti-tetanus antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)

### 7.3.3. Antibody response to PT, FHA and PRN

The results are detailed in the following table and figures:

Table 54 Anti-PT, anti-FHA and anti-PRN antibody GMC and seropositivity rates at one month post dose 3 of DTPa of vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

Table 55 Vaccine response for anti-PT and anti-FHA antibodies at one month post dose 3 of DTPa vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

Table 56 Vaccine response for Anti-PRN antibody at one month post dose 3 of DTPa vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

Figure 26 Reverse cumulative curves for anti-FHA antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)

Figure 27 Reverse cumulative curves for anti-PT antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)

Figure 28 Reverse cumulative curves for anti PRN concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)

### 7.3.4. Antibody response to poliovirus types 1, 2 and 3

The results are detailed in the following table and figures:

Table 57 Anti-Poliovirus 1, 2 and 3 antibody GMT and seroprotection rates at two months post dose 3 of OPV vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

## 7.4. Immunogenicity summary

***Anti-rotavirus IgA antibody response***

Immunogenicity sub cohort 1:

- Anti-rotavirus IgA antibody seroconversion rate was 74.7% [95% CI: 68.9%; 79.9%] in the HRV group, one month post-Dose 2 of HRV vaccination. Anti-rotavirus IgA seropositivity rate was 3.5% [95% CI: 1.6%; 6.6%] subjects in the Placebo group, one month post-Dose 2 of placebo.
- Anti-rotavirus IgA antibody GMCs in overall subjects was 90.2 U/ml [95% CI: 73.3; 111.1] in the HRV group and < 20 U/ml in the placebo group, one month post-Dose 2 of HRV vaccine/placebo.
- Anti-rotavirus IgA antibody seropositivity rate was 71.5% [95% CI: 65.5%; 77.1%] in the HRV group, at approximately one year of age. Anti-rotavirus IgA seropositivity rate was 46.8% [95% CI: 40.5%; 53.2%] in the Placebo group, at approximately one year of age.
- Anti-rotavirus IgA antibody GMCs in overall subjects was 66.5 U/ml [95% CI: 54.6; 81.0] in the HRV group and 35.3 U/ml [95% CI: 29.3; 42.5] in the placebo group, at approximately one year of age.

Immunogenicity sub cohort 2:

- Anti-rotavirus IgA antibody seroconversion rate was 64.2% (95% CI: 55.4%; 72.3%) in the HRV group, one month post-Dose 2 of HRV vaccine co-administered with childhood vaccinations. Anti-rotavirus IgA seropositivity rate was 9.4% (95% CI: 5.1%; 15.5%) in the Placebo group, one month post-Dose 2 of placebo.
- Anti-rotavirus IgA antibody GMCs in overall subjects were 84.0 U/ml [95% CI: 58.9; 119.8] in the HRV group and < 20 U/ml in the placebo group, at one month post-Dose 2 of HRV vaccine/placebo.
- Anti-rotavirus IgA antibody seropositivity rate was 50.0% (95% CI: 40.9%; 59.1%) in the HRV group, at approximately one year of age. Anti-rotavirus IgA seropositivity rate was 21.8% (95% CI: 15.1%; 29.8%) in the Placebo group, at approximately one year of age.
- Anti-rotavirus IgA antibody GMCs in overall subjects was 31.3 U/ml [95% CI: 24.6; 39.8] in the HRV group and <20 U/ml in the placebo group, at approximately 1 year of age.

***Antibody response to diphtheria toxoid and tetanus toxoid***

- The anti-diphtheria and anti-tetanus antibody seroprotection rates (defined as antibody concentrations ≥ 0.1 IU/ml) was 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, one month post-Dose 3 of DTPa vaccine.
- At one month post-dose 3 of DTPa vaccine, the anti-diphtheria antibody GMCs reported for the HRV group was 0.375 IU/ml [95% CI: 0.326; 0.432] and for the Placebo group was 0.334 IU/ml [95% CI: 0.308; 0.363].
- At one month post-dose 3 of DTPa vaccine, the anti-tetanus antibody GMCs reported for the HRV group was 1.281 IU/ml [95% CI: 1.253; 1.309] and for the Placebo group was 1.343 IU/ml [95% CI: 1.215; 1.486].

***Antibody response to PT, FHA and PRN***

- The anti-PT, anti-FHA, and anti-PRN antibody seropositivity rates (defined as antibody concentrations ≥ 5 EL.U/ml) were 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, one month post-Dose 3 of DTPa vaccine.
- At one month post-dose 3 of DTPa vaccine, the anti-PT antibody GMCs reported for the HRV group was 88.9 U/ml [95% CI: 84.9; 93.2] and for the Placebo group was 90.5 U/ml [95% CI: 86.4; 94.8].
- At one month post-dose 3 of DTPa vaccine, the anti-FHA antibody GMCs reported for the HRV group was 59.5 U/ml [95% CI: 55.8; 63.5] and for the Placebo group was 65.8 U/ml [95% CI: 61.3; 70.5].
- At one month post-dose 3 of DTPa vaccine, the anti-PRN antibody GMCs reported for the HRV group was 41.9 U/ml [95% CI: 37.6; 46.5] and for the Placebo group was 50.8 U/ml [95% CI: 44.3; 58.1].

***Antibody response to poliovirus types 1, 2 and 3***

- Anti-poliovirus type 1 and anti-poliovirus type 2 seroprotection rates (defined as antibody titres ≥ 8 $ED_{50}$) were 100.0% [95% CI: 97.3%; 100%] in the HRV group and 100.0% [95% CI: 97.4%; 100%] in the placebo group, two months post-Dose 3 of OPV vaccine.
- Anti-poliovirus type 3 seroprotection rate (defined as antibody titres ≥ 8 $ED_{50}$) was 99.3% [95% CI: 96.0%; 100%] in the HRV group and 99.3% [95% CI: 96.1%; 100%] in the placebo group, two months post-Dose 3 of OPV vaccine.
- At two months post-dose 3 of OPV vaccine, the anti-Polio 1 antibody GMTs reported for the HRV group was 2101.1 [95% CI: 1734.8; 2544.8] and for the Placebo group was 2259.4 [95% CI: 1844.4; 2767.9].
- At two months post-dose 3 of OPV vaccine, the anti-Polio 2 antibody GMTs reported for the HRV group was 402.5 [95% CI: 334.8; 483.9] and for the Placebo group was 425.1 [95% CI: 371.0; 487.1].

- At two months post-dose 3 of OPV vaccine, the anti-Polio 3 antibody GMTs reported for the HRV group was 426.6 [95% CI: 342.7; 531.0] and for the Placebo group was 360.3 [95% CI: 303.0; 428.3]Overall

# 8. CONCLUSIONS (SUMMARY)

- Two doses of GSK Biologicals' oral live attenuated liquid HRV vaccine was immunogenic in Chinese infants as evidenced by the anti-rotavirus IgA antibody seroconversion rate and GMCs at one month post Dose 2. The immune response persisted at one year of age as shown by the anti-rotavirus IgA antibody seropositivity rate and GMCs at approximately one year of age.
- Two doses of GSK Biologicals' oral live attenuated liquid HRV vaccine did not appear to impact the immunogenicity of the co-administered DTPa vaccine and Oral Poliovirus vaccine [OPV].

# 9. TABLES AND FIGURES

## 9.1. Subject eligibility and attrition from the study

### 9.1.1. Number of subjects

**Table 9 Number of subjects by center (Total vaccinated cohort – Immunogenicity cohort)**

| | HRV | Placebo | Total | |
|---|---|---|---|---|
| **Center** | **n** | **n** | **n** | **%** |
| [redacted] | 105 | 102 | 207 | 22.5 |
| | 99 | 101 | 200 | 21.8 |
| | 102 | 103 | 205 | 22.3 |
| | 153 | 153 | 306 | 33.3 |
| All | 459 | 459 | 918 | 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

### 9.1.2. Study completion and withdrawal from study

**Table 10 Number of subjects entered, completed and withdrawn with reason for withdrawal till Visit 7 (Total vaccinated cohort)**

| | HRV | Placebo | Total |
|---|---|---|---|
| **Number of subjects vaccinated** | 1666 | 1667 | 3333 |
| **Number of subjects completed** | 1518 | 1499 | 3017 |
| **Number of subjects withdrawn** | 148 | 168 | 316 |
| **Reasons for withdrawal :** | | | |
| Serious Adverse Event | 6 | 7 | 13 |
| Non-Serious Adverse Event | 4 | 8 | 12 |
| Protocol violation | 0 | 0 | 0 |
| Consent withdrawal (not due to an adverse event) | 55 | 46 | 101 |
| Migrated/moved from study area | 23 | 24 | 47 |
| Lost to follow-up (subjects with incomplete vaccination course) | 0 | 0 | 0 |
| Lost to follow-up (subjects with complete vaccination course) | 0 | 0 | 0 |
| Sponsor study termination | 0 | 0 | 0 |
| Other - diarrhea | 1 | 0 | 1 |
| Other - not willing to participate in the extended follow-up* (Visit 7) | 59 | 83 | 142 |

Vaccinated= number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
*Second year follow up

## 9.1.3. Protocol deviations

### 9.1.3.1. Protocol Deviations leading to elimination from ATP analyses

**Table 11 Number of subjects enrolled into the study as well as the number excluded from ATP cohort for immunogenicity with reasons for exclusion**

| | Total | | | HRV | | Placebo | | NOGRP | |
|---|---|---|---|---|---|---|---|---|---|
| **Title** | **n** | **s** | **%** | **n** | **s** | **n** | **s** | **n** | **s** |
| Total cohort | 3340 | | | 1667 | | 1667 | | 6 | |
| Study vaccine dose not administrated but subject number allocated ( code 1030 ) | 7 | 7 | | 1 | 1 | 0 | 0 | 6 | 6 |
| Total vaccinated cohort | 3333 | | 100 | 1666 | | 1667 | | 0 | |
| Administration of vaccine(s) forbidden in the protocol ( code 1040 ) | 2 | 2 | | 1 | 1 | 1 | 1 | 0 | 0 |
| Randomisation code broken at the investigator site ( code 1060 ) | 2 | 2 | | 0 | 0 | 2 | 2 | 0 | 0 |
| Study vaccine dose not administered according to protocol ( code 1070 ) | 41 | 41 | | 22 | 22 | 19 | 19 | 0 | 0 |
| ATP cohort for safety | 3288 | | 98.6 | 1643 | | 1645 | | 0 | |
| Protocol violation (inclusion/exclusion criteria) ( code 2010 ) | 7 | 7 | | 5 | 5 | 2 | 2 | 0 | 0 |
| Initially seropositive or initially unknown antibody status ( code 2020 ) | 24 | 24 | | 10 | 10 | 14 | 14 | 0 | 0 |
| Administration of any medication forbidden by the protocol ( code 2040 ) | 2 | 8 | | 1 | 6 | 1 | 2 | 0 | 0 |
| Concomitant infection related to the vaccine which may influence immune response ( code 2060 ) | 3 | 4 | | 1 | 1 | 2 | 3 | 0 | 0 |
| Non compliance with vaccination schedule ( including wrong and unknown dates ) ( code 2080 ) | 3 | 5 | | 2 | 2 | 1 | 3 | 0 | 0 |
| Non compliance with blood sampling schedule ( including wrong and unknown dates ( code 2090 ) | 7 | 7 | | 5 | 5 | 2 | 2 | 0 | 0 |
| Essential serological data missing ( code 2100 ) | 64 | 68 | | 33 | 35 | 31 | 33 | 0 | 0 |
| Subject not planned to be bled for their all blood sampling visits ( code 2130 ) | 2394 | 2415 | | 1195 | 1207 | 1199 | 1208 | 0 | 0 |
| ATP cohort for immunogenicity | 784 | | 23.5 | 391 | | 393 | | 0 | |

NOGRP = No assigned group
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 Number of subjects enrolled into the study as well as the number of subjects excluded from the ATP cohort for immunogenicity (sub cohort 2) - co-administered vaccination with reasons for exclusion

| | Total | | | HRV | | Placebo | | NOGRP | |
|---|---|---|---|---|---|---|---|---|---|
| **Title** | **n** | **s** | **%** | **n** | **s** | **n** | **s** | **n** | **s** |
| Total number of subjects enrolled in immunogenicity sub cohort 2 | 312 | | | 153 | | 153 | | 6 | |
| Study vaccine dose not administrated but subject number allocated ( code 1030 ) | 6 | 6 | | 0 | 0 | 0 | 0 | 6 | 6 |
| Total number of subjects in immunogenicity sub cohort 2 receiving at least one dose of study vaccines | 306 | | 100 | 153 | | 153 | | 0 | |
| 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 ) | 8 | 8 | | 5 | 5 | 3 | 3 | 0 | 0 |
| Protocol violation (inclusion/exclusion criteria) ( code 2010 ) | 1 | 1 | | 0 | 0 | 1 | 1 | 0 | 0 |
| Administration of any medication forbidden by the protocol ( code 2040 ) | 1 | 1 | | 1 | 1 | 0 | 0 | 0 | 0 |
| Concomitant infection related to the vaccine which may influence immune response ( code 2060 ) | 3 | 3 | | 1 | 1 | 2 | 2 | 0 | 0 |
| Non compliance with vaccination schedule ( including wrong and unknown dates ) ( code 2080 ) | 3 | 5 | | 3 | 3 | 0 | 2 | 0 | 0 |
| Non compliance with blood sampling schedule ( including wrong and unknown dates ( code 2090 ) | 2 | 3 | | 0 | 1 | 2 | 2 | 0 | 0 |
| Essential serological data missing ( code 2100 ) | 11 | 11 | | 6 | 6 | 5 | 5 | 0 | 0 |
| Incomplete vaccination to OPV & DTP-any of the 3 dose of these vaccines not received ( code 2500 ) | 1 | 10 | | 1 | 5 | 0 | 5 | 0 | 0 |
| ATP cohort for immunogenicity (sub cohort 2) - co-administered vaccination | 275 | | 89.9 | 136 | | 139 | | 0 | |

NOGRP = No assigned group
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 number of subjects in immunogenicity sub cohort 2 receiving at least one dose of study vaccines

## Table 13 Deviations from specifications for age and intervals between study visits (ATP cohort for immunogenicity – sub cohort 1)

| | | Age at Dose 1 of HRV/placebo | VIS01 D 0-Dose:1 of HRV/placebo | Dose:1 of HRV/placebo-Dose:2 of HRV/placebo | | Dose:2 of HRV/placebo-VIS03 M 2 | | DOB-VIS06 M 12 | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** |
| | | from 6 to 16 weeks | from 0 to 0 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 351 to 379 days | from 335 to 395 days |
| HRV | N | 257 | 257 | 257 | 257 | 257 | 257 | 253 | 253 |
| | n | 0 | 1 | 2 | 0 | 9 | 0 | 12 | 0 |
| | % | 0.0 | 0.4 | 0.8 | 0.0 | 3.5 | 0.0 | 4.7 | 0.0 |
| | range | 6 to 15 | 0 to 6 | 28 to 47 | 28 to 47 | 24 to 47 | 24 to 47 | 350 to 393 | 350 to 393 |
| Placebo | N | 254 | 254 | 254 | 254 | 254 | 254 | 253 | 253 |
| | n | 0 | 0 | 0 | 0 | 9 | 0 | 8 | 2 |
| | % | 0.0 | 0.0 | 0.0 | 0.0 | 3.5 | 0.0 | 3.2 | 0.8 |
| | range | 6 to 15 | 0 to 0 | 30 to 42 | 30 to 42 | 21 to 47 | 21 to 47 | 350 to 408 | 350 to 408 |

Adapted = interval used for defining the ATP cohort 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
VIS01 D 0= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2
VIS06 M 12= Blood sample taken at year 1 of age

## Table 14 Deviations from specifications for age and intervals between study visits (ATP cohort for immunogenicity (sub cohort 2) - anti-RV IgA)

| | | Age at Dose 1 of HRV/placebo | VIS01 D 0-Dose:1 of HRV/placebo | Dose:1 of HRV/placebo-Dose:2 of HRV/placebo | | Dose:2 of HRV/placebo-VIS03 M 2 | | DOB-VIS06 M 12 | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** |
| | | from 6 to 16 weeks | from 0 to 0 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 351 to 379 days | from 335 to 395 days |
| HRV | N | 134 | 134 | 134 | 134 | 134 | 134 | 125 | 125 |
| | n | 0 | 0 | 7 | 0 | 8 | 0 | 15 | 1 |
| | % | 0.0 | 0.0 | 5.2 | 0.0 | 6.0 | 0.0 | 12.0 | 0.8 |
| | range | 8 to 12 | 0 to 0 | 28 to 46 | 28 to 46 | 28 to 48 | 28 to 48 | 345 to 442 | 345 to 442 |
| Placebo | N | 139 | 139 | 139 | 139 | 139 | 139 | 134 | 134 |
| | n | 0 | 0 | 14 | 0 | 9 | 0 | 14 | 1 |
| | % | 0.0 | 0.0 | 10.1 | 0.0 | 6.5 | 0.0 | 10.4 | 0.7 |
| | range | 8 to 12 | 0 to 0 | 28 to 46 | 28 to 46 | 28 to 48 | 28 to 48 | 340 to 400 | 340 to 400 |

Adapted = interval used for defining the ATP cohort 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
VIS01 D 0= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2
VIS06 M 12= Blood sample taken at year 1 of age

## Table 15 Deviations from specifications for age and intervals between study visits (ATP cohort for immunogenicity (sub cohort 2) - co-administered vaccination)

| | | Age at Dose 1 of OPV vaccine | VIS01 D 0 of OPV vaccine-Dose:1 of OPV vaccine | Dose:1 of OPV vaccine-Dose:2 of OPV vaccine | | Dose:2 of OPV vaccine-Dose:3 of OPV vaccine | | Dose:3 of OPV vaccine-VIS04 M 3 | | VIS04 M 3-VIS05 M 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** |
| | | from 6 to 16 weeks | from 0 to 0 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days |
| HRV | N | 136 | 136 | 136 | 136 | 136 | 136 | 136 | 136 | 136 | 136 |
| | n | 0 | 0 | 8 | 0 | 8 | 0 | 27 | 0 | 41 | 0 |
| | % | 0.0 | 0.0 | 5.9 | 0.0 | 5.9 | 0.0 | 19.9 | 0.0 | 30.1 | 0.0 |
| | range | 8 to 12 | 0 to 0 | 28 to 46 | 28 to 46 | 28 to 48 | 28 to 48 | 28 to 47 | 28 to 47 | 23 to 48 | 23 to 48 |
| Placebo | N | 139 | 139 | 139 | 139 | 139 | 139 | 139 | 139 | 139 | 139 |
| | n | 0 | 0 | 15 | 0 | 9 | 0 | 29 | 0 | 36 | 0 |
| | % | 0.0 | 0.0 | 10.8 | 0.0 | 6.5 | 0.0 | 20.9 | 0.0 | 25.9 | 0.0 |
| | range | 8 to 12 | 0 to 0 | 28 to 46 | 28 to 46 | 28 to 48 | 28 to 48 | 28 to 48 | 28 to 48 | 21 to 48 | 21 to 48 |

Adapted = interval used for defining the ATP cohort for immunogenicity (sub cohort 2) - co-administered vaccination
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
VIS01 D 0= Blood sample taken prior to dose 1
VIS04 M 3= Dose 3 of DTPa at Visit 4 at Month 3
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

## Table 16 Deviations from specifications for age and intervals between study visits (Total vaccinated cohort - Immunogenicity sub cohort 1)

| | | Age at Dose 1 of HRV/placebo | VIS01 D 0-Dose:1 of HRV/placebo | Dose:1 of HRV/placebo-Dose:2 of HRV/placebo | | Dose:2 of HRV/placebo-VIS03 M 2 | | DOB-VIS06 M 12 | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** |
| | | from 6 to 16 weeks | from 0 to 0 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 351 to 379 days | from 335 to 395 days |
| HRV | N | 306 | 306 | 288 | 288 | 281 | 281 | 278 | 278 |
| | n | 1 | 1 | 3 | 1 | 13 | 4 | 13 | 0 |
| | % | 0.3 | 0.3 | 1.0 | 0.3 | 4.6 | 1.4 | 4.7 | 0.0 |
| | range | 5 to 16 | 0 to 6 | 28 to 51 | 28 to 51 | 18 to 87 | 18 to 87 | 350 to 393 | 350 to 393 |
| Placebo | N | 306 | 306 | 287 | 287 | 279 | 279 | 282 | 282 |
| | n | 0 | 0 | 1 | 1 | 11 | 2 | 11 | 3 |
| | % | 0.0 | 0.0 | 0.3 | 0.3 | 3.9 | 0.7 | 3.9 | 1.1 |
| | range | 6 to 15 | 0 to 0 | 30 to 90 | 30 to 90 | 18 to 75 | 18 to 75 | 350 to 449 | 350 to 449 |

Adapted = interval used for defining the ATP cohort 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
VIS01 D 0= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2
VIS06 M 12= Blood sample taken at year 1 of age

## Table 17 Deviations from specifications for age and intervals between study visits - HRV vaccination (Total vaccinated cohort - Immunogenicity sub cohort 2)

| | | Age at Dose 1 of HRV/placebo | VIS01 D 0-Dose:1 of HRV/placebo | Dose:1 of HRV/placebo-Dose:2 of HRV/placebo | | Dose:2 of HRV/placebo-VIS03 M 2 | | DOB-VIS06 M 12 | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** |
| | | from 6 to 16 weeks | from 0 to 0 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 351 to 379 days | from 335 to 395 days |
| HRV | N | 153 | 153 | 150 | 150 | 148 | 148 | 139 | 139 |
| | n | 0 | 0 | 12 | 1 | 11 | 1 | 17 | 1 |
| | % | 0.0 | 0.0 | 8.0 | 0.7 | 7.4 | 0.7 | 12.2 | 0.7 |
| | range | 8 to 12 | 0 to 0 | 28 to 50 | 28 to 50 | 20 to 48 | 20 to 48 | 345 to 442 | 345 to 442 |
| Placebo | N | 153 | 153 | 151 | 151 | 150 | 150 | 145 | 145 |
| | n | 0 | 0 | 17 | 2 | 10 | 0 | 16 | 1 |
| | % | 0.0 | 0.0 | 11.3 | 1.3 | 6.7 | 0.0 | 11.0 | 0.7 |
| | range | 8 to 12 | 0 to 0 | 28 to 56 | 28 to 56 | 28 to 48 | 28 to 48 | 340 to 400 | 340 to 400 |

Adapted = interval used for defining the ATP cohort 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
VIS01 D 0= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2
VIS06 M 12= Blood sample taken at year 1 of age

## Table 18 Deviations from specifications for age and intervals between study visits - co-administered vaccines (Total vaccinated cohort - Immunogenicity sub cohort 2)

| | | Age at Dose 1 of OPV vaccine | VIS01 D 0-Dose:1 of OPV vaccine | Dose:1 of OPV vaccine-Dose:2 of OPV vaccine | | Dose:2 of OPV vaccine-Dose:3 of OPV vaccine | | Dose:3 of OPV vaccine- VIS04 M 3 | | VIS04 M 3-VIS05 M 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Group** | | **Protocol** | **Protocol** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** | **Protocol** | **Adapted** |
| | | from 6 to 16 weeks | from 0 to 0 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days | from 30 to 48 days | from 21 to 48 days |
| HRV | N | 153 | 153 | 150 | 150 | 149 | 149 | 148 | 148 | 146 | 146 |
| | n | 0 | 0 | 12 | 1 | 10 | 0 | 29 | 2 | 44 | 1 |
| | % | 0.0 | 0.0 | 8.0 | 0.7 | 6.7 | 0.0 | 19.6 | 1.4 | 30.1 | 0.7 |
| | range | 8 to 12 | 0 to 0 | 28 to 50 | 28 to 50 | 28 to 48 | 28 to 48 | 28 to 66 | 28 to 66 | 23 to 147 | 23 to 147 |
| Placebo | N | 153 | 153 | 151 | 151 | 150 | 150 | 148 | 148 | 148 | 148 |
| | n | 0 | 0 | 17 | 2 | 10 | 0 | 33 | 0 | 40 | 2 |
| | % | 0.0 | 0.0 | 11.3 | 1.3 | 6.7 | 0.0 | 22.3 | 0.0 | 27.0 | 1.4 |
| | range | 8 to 12 | 0 to 0 | 28 to 56 | 28 to 56 | 28 to 48 | 28 to 48 | 28 to 48 | 28 to 48 | 21 to 57 | 21 to 57 |

Adapted = interval used for defining the ATP cohort for immunogenicity (sub cohort 2) - co-administered vaccination
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
VIS01 D 0= Blood sample taken prior to dose 1
VIS04 M 3= Dose 3 of DTPa at Visit 4 at Month 3
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

#### 9.1.3.2. Protocol Deviations not leading to elimination from ATP analyses

Protocol deviations not leading to elimination from ATP analyses have been presented in the report dated 29-OCT-2012.

## 9.2. Demographic characteristics

### 9.2.1. ATP cohort for immunogenicity

**Table 19 Summary of demographic characteristics (ATP cohort for immunogenicity)**

| | | HRV N = 391 | | Placebo N = 393 | | Total N = 784 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 10.0 | - | 10.1 | - | 10.0 | - |
| | SD | 2.52 | - | 2.42 | - | 2.47 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 6 | - | 6 | - | 6 | - |
| | Maximum | 15 | - | 15 | - | 15 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.5 | - | 14.5 | - | 14.5 | - |
| | SD | 2.60 | - | 2.47 | - | 2.53 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 10 | - | 10 | - | 10 | - |
| | Maximum | 22 | - | 21 | - | 22 | - |
| Gender | Female | 196 | 50.1 | 198 | 50.4 | 394 | 50.3 |
| | Male | 195 | 49.9 | 195 | 49.6 | 390 | 49.7 |
| Geographic Ancestry | Asian-Chinese heritage | 391 | 100 | 393 | 100 | 784 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 20 Summary of demographic characteristics (ATP cohort for immunogenicity - sub cohort 1)

| | | HRV N = 257 | | Placebo N = 254 | | Total N = 511 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 10.1 | - | 10.0 | - | 10.1 | - |
| | SD | 2.96 | - | 2.85 | - | 2.90 | - |
| | Median | 10.0 | - | 9.0 | - | 10.0 | - |
| | Minimum | 6 | - | 6 | - | 6 | - |
| | Maximum | 15 | - | 15 | - | 15 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.6 | - | 14.5 | - | 14.6 | - |
| | SD | 3.07 | - | 2.91 | - | 2.99 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 10 | - | 10 | - | 10 | - |
| | Maximum | 22 | - | 21 | - | 22 | - |
| Gender | Female | 131 | 51.0 | 122 | 48.0 | 253 | 49.5 |
| | Male | 126 | 49.0 | 132 | 52.0 | 258 | 50.5 |
| Geographic Ancestry | Asian-Chinese heritage | 257 | 100 | 254 | 100 | 511 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 21 Summary of demographic characteristics (ATP cohort for immunogenicity (sub cohort 2) – anti-RV IgA)

| | | HRV N = 134 | | Placebo N = 139 | | Total N = 273 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.8 | - | 10.1 | - | 10.0 | - |
| | SD | 1.30 | - | 1.31 | - | 1.31 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 8 | - | 8 | - | 8 | - |
| | Maximum | 12 | - | 12 | - | 12 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.3 | - | 14.6 | - | 14.5 | - |
| | SD | 1.28 | - | 1.31 | - | 1.30 | - |
| | Median | 14.0 | - | 15.0 | - | 14.0 | - |
| | Minimum | 12 | - | 12 | - | 12 | - |
| | Maximum | 17 | - | 17 | - | 17 | - |
| Gender | Female | 65 | 48.5 | 76 | 54.7 | 141 | 51.6 |
| | Male | 69 | 51.5 | 63 | 45.3 | 132 | 48.4 |
| Geographic Ancestry | Asian-Chinese heritage | 134 | 100 | 139 | 100 | 273 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 22 Summary of demographic characteristics (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

| | | HRV N = 136 | | Placebo N = 139 | | Total N = 275 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of OPV vaccine | Mean | 9.8 | - | 10.1 | - | 10.0 | - |
| | SD | 1.30 | - | 1.31 | - | 1.31 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 8 | - | 8 | - | 8 | - |
| | Maximum | 12 | - | 12 | - | 12 | - |
| Age (weeks) at vaccination dose 2 of OPV vaccine/dose 1 of DTPa vaccine | Mean | 14.3 | - | 14.6 | - | 14.5 | - |
| | SD | 1.29 | - | 1.32 | - | 1.31 | - |
| | Median | 14.0 | - | 15.0 | - | 14.0 | - |
| | Minimum | 12 | - | 12 | - | 12 | - |
| | Maximum | 17 | - | 17 | - | 17 | - |
| Age (weeks) at vaccination dose 3 of OPV vaccine/dose 2 of DTPa vaccine | Mean | 18.8 | - | 19.1 | - | 19.0 | - |
| | SD | 1.45 | - | 1.41 | - | 1.44 | - |
| | Median | 19.0 | - | 19.0 | - | 19.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 22 | - | 23 | - |
| Age (weeks) at vaccination dose 3 of DTPa vaccine | Mean | 23.2 | - | 23.7 | - | 23.5 | - |
| | SD | 1.59 | - | 1.55 | - | 1.58 | - |
| | Median | 23.0 | - | 24.0 | - | 23.0 | - |
| | Minimum | 21 | - | 21 | - | 21 | - |
| | Maximum | 28 | - | 28 | - | 28 | - |
| Gender | Female | 64 | 47.1 | 74 | 53.2 | 138 | 50.2 |
| | Male | 72 | 52.9 | 65 | 46.8 | 137 | 49.8 |
| Geographic Ancestry | Asian-Chinese heritage | 136 | 100 | 139 | 100 | 275 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## 9.2.2. Total vaccinated cohort (Secondary analysis)

### Table 23 Summary of demographic characteristics (Total Vaccinated cohort – Immunogenicity cohort)

| | | HRV N = 459 | | Placebo N = 459 | | Total N = 918 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 10.1 | - | 10.1 | - | 10.1 | - |
| | SD | 2.54 | - | 2.41 | - | 2.48 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 5 | - | 6 | - | 5 | - |
| | Maximum | 16 | - | 15 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.6 | - | 14.6 | - | 14.6 | - |
| | SD | 2.62 | - | 2.49 | - | 2.56 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 10 | - | 10 | - | 10 | - |
| | Maximum | 23 | - | 22 | - | 23 | - |
| | Unknown | 21 | - | 21 | - | 42 | - |
| Gender | Female | 225 | 49.0 | 235 | 51.2 | 460 | 50.1 |
| | Male | 234 | 51.0 | 224 | 48.8 | 458 | 49.9 |
| Geographic Ancestry | Asian-Chinese heritage | 459 | 100 | 459 | 100 | 918 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

# 9.3. Immunogenicity results

## 9.3.1. According-to-protocol analysis

### 9.3.1.1. Anti-rotavirus IgA antibody response

**Table 24 Anti-rotavirus IgA antibody GMC, seroconversion rate at Visit 3 and seropositivity rate at Visit 6 (ATP cohort for immunogenicity)**

| | | | | ≥ 20 U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Cohort | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| Immunogenicity sub cohort 1 | HRV | PRE | 257 | 0 | 0.0 | 0.0 | 1.4 | <20.0 | - | - |
| | | VIS03 M 2 | 257 | 192 | 74.7 | 68.9 | 79.9 | 90.2 | 73.3 | 111.1 |
| | | VIS06 M 12 | 246 | 176 | 71.5 | 65.5 | 77.1 | 66.5 | 54.6 | 81.0 |
| | Placebo | PRE | 254 | 0 | 0.0 | 0.0 | 1.4 | <20.0 | - | - |
| | | VIS03 M 2 | 254 | 9 | 3.5 | 1.6 | 6.6 | <20.0 | - | - |
| | | VIS06 M 12 | 252 | 118 | 46.8 | 40.5 | 53.2 | 35.3 | 29.3 | 42.5 |
| Immunogenicity sub cohort 2 | HRV | PRE | 134 | 0 | 0.0 | 0.0 | 2.7 | <20.0 | - | - |
| | | VIS03 M 2 | 134 | 86 | 64.2 | 55.4 | 72.3 | 84.0 | 58.9 | 119.8 |
| | | VIS06 M 12 | 124 | 62 | 50.0 | 40.9 | 59.1 | 31.3 | 24.6 | 39.8 |
| | Placebo | PRE | 139 | 0 | 0.0 | 0.0 | 2.6 | <20.0 | - | - |
| | | VIS03 M 2 | 139 | 13 | 9.4 | 5.1 | 15.5 | <20.0 | - | - |
| | | VIS06 M 12 | 133 | 29 | 21.8 | 15.1 | 29.8 | <20.0 | - | - |
| Immunogenicity cohort | HRV | PRE | 391 | 0 | 0.0 | 0.0 | 0.9 | <20.0 | - | - |
| | | VIS03 M 2 | 391 | 278 | 71.1 | 66.3 | 75.5 | 88.0 | 73.4 | 105.6 |
| | | VIS06 M 12 | 370 | 238 | 64.3 | 59.2 | 69.2 | 51.6 | 44.1 | 60.5 |
| | Placebo | PRE | 393 | 0 | 0.0 | 0.0 | 0.9 | <20.0 | - | - |
| | | VIS03 M 2 | 393 | 22 | 5.6 | 3.5 | 8.4 | <20.0 | - | - |
| | | VIS06 M 12 | 385 | 147 | 38.2 | 33.3 | 43.2 | 27.4 | 23.7 | 31.7 |

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2 of HRV/Placebo
VIS06 M 12= Blood sample taken at year 1 of age
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

## Table 25 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies at Visit 3 and at Visit 6 (ATP cohort for immunogenicity)

| | | | | GMC | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| Cohort | Group | Timing | N | value | LL | UL |
| Immunogenicity sub cohort 1 | HRV | VIS03 M 2 | 192 | 189.9 | 158.3 | 227.9 |
| | | VIS06 M 12 | 176 | 141.3 | 118.0 | 169.1 |
| | Placebo | VIS03 M 2 | 9 | 134.4 | 58.3 | 309.7 |
| | | VIS06 M 12 | 118 | 148.1 | 124.4 | 176.4 |
| Immunogenicity sub cohort 2 | HRV | VIS03 M 2 | 86 | 275.8 | 193.1 | 393.8 |
| | | VIS06 M 12 | 62 | 97.8 | 75.0 | 127.6 |
| | Placebo | VIS03 M 2 | 13 | 255.5 | 105.9 | 616.7 |
| | | VIS06 M 12 | 29 | 112.6 | 67.7 | 187.4 |
| Immunogenicity cohort | HRV | VIS03 M 2 | 278 | 213.2 | 180.3 | 252.0 |
| | | VIS06 M 12 | 238 | 128.4 | 110.5 | 149.2 |
| | Placebo | VIS03 M 2 | 22 | 196.4 | 108.9 | 354.3 |
| | | VIS06 M 12 | 147 | 140.3 | 118.4 | 166.4 |

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
VIS03 M 2= Blood sample taken 1 month after dose 2 of HRV/Placebo
VIS06 M 12= Blood sample taken at year 1 of age
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

## Table 26 Anti-rotavirus IgA antibody GMC and seropositivity rates at Visit 6 excluding subjects who had RVGE between Visit 1 and Visit 6 (ATP cohort for immunogenicity)

| | | | | ≥ 20 U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Cohort | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| Immunogenicity sub cohort 1 | HRV | VIS06 M 12 | 239 | 170 | 71.1 | 64.9 | 76.8 | 65.0 | 53.3 | 79.4 |
| | Placebo | VIS06 M 12 | 235 | 103 | 43.8 | 37.4 | 50.4 | 32.0 | 26.5 | 38.7 |
| Immunogenicity sub cohort 2 | HRV | VIS06 M 12 | 124 | 62 | 50.0 | 40.9 | 59.1 | 31.3 | 24.6 | 39.8 |
| | Placebo | VIS06 M 12 | 129 | 25 | 19.4 | 13.0 | 27.3 | <20.0 | - | - |
| Immunogenicity cohort | HRV | VIS06 M 12 | 363 | 232 | 63.9 | 58.7 | 68.9 | 50.6 | 43.2 | 59.3 |
| | Placebo | VIS06 M 12 | 364 | 128 | 35.2 | 30.3 | 40.3 | 25.1 | 21.7 | 28.9 |

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
VIS06 M 12= Blood sample taken at year 1 of age
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

## Table 27 Percentage of subjects with antiviral medication from dose 1 till Visit 3 (ATP cohort for immunogenicity)

| | | HRV N = 391 | | Placebo N = 393 | |
|---|---|---|---|---|---|
| **Medication** | **Parameters or Categories** | **n** | **%** | **n** | **%** |
| Antiviral received | No | 371 | 94.9 | 366 | 93.1 |
| | Yes | 20 | 5.1 | 27 | 6.9 |

N = number of subjects in a given group
n/% = number / percentage of subjects antiviral received or not

## Table 28 Anti-rotavirus IgA antibody GMC and seroconversion rate at Visit 3 by antiviral medication status (ATP cohort for immunogenicity)

| | | | | ≥ 20 U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| **Medication** | **Group** | **Timing** | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** |
| Antiviral received | HRV | PRE | 20 | 0 | 0.0 | 0.0 | 16.8 | <20.0 | - | - |
| | | VIS03 M 2 | 20 | 12 | 60.0 | 36.1 | 80.9 | 88.3 | 32.9 | 236.8 |
| | Placebo | PRE | 27 | 0 | 0.0 | 0.0 | 12.8 | <20.0 | - | - |
| | | VIS03 M 2 | 27 | 3 | 11.1 | 2.4 | 29.2 | <20.0 | - | - |
| Antiviral not received | HRV | PRE | 371 | 0 | 0.0 | 0.0 | 1.0 | <20.0 | - | - |
| | | VIS03 M 2 | 371 | 266 | 71.7 | 66.8 | 76.2 | 88.0 | 73.1 | 106.0 |
| | Placebo | PRE | 366 | 0 | 0.0 | 0.0 | 1.0 | <20.0 | - | - |
| | | VIS03 M 2 | 366 | 19 | 5.2 | 3.2 | 8.0 | <20.0 | - | - |

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
VIS03 M 2= Blood sample taken 1 month after dose 2 of HRV/Placebo

## Table 29 Difference between groups in percentage of subjects who seroconverted at Visit 3 for serum anti-rotavirus IgA antibody (ATP cohort for immunogenicity)

| **Cohort** | | | | | | | **Difference in seroconversion rate (HRV minus Placebo)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **HRV** | | | **Placebo** | | | | **95% CI** | |
| | **N** | **n** | **%** | **N** | **n** | **%** | **%** | **LL** | **UL** |
| Immunogenicity sub cohort 1 | 257 | 192 | 74.7 | 254 | 9 | 3.5 | 71.16 | 64.97 | 76.52 |
| Immunogenicity sub cohort 2 | 134 | 86 | 64.2 | 139 | 13 | 9.4 | 54.83 | 44.80 | 63.66 |
| Immunogenicity cohort | 391 | 278 | 71.1 | 393 | 22 | 5.6 | 65.50 | 60.22 | 70.28 |

N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentration ≥ 20 U/ml
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

**Table 30 Difference between groups in percentage of subjects who were seropositive at Visit 6 for serum anti-rotavirus IgA antibody (ATP cohort for immunogenicity)**

| Cohort | | | | | | | Difference in seropositive rate (HRV minus Placebo) | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV | | | Placebo | | | | 95% CI | |
| | N | n | % | N | n | % | % | LL | UL |
| Immunogenicity sub cohort 1 | 246 | 176 | 71.5 | 252 | 118 | 46.8 | 24.72 | 16.21 | 32.87 |
| Immunogenicity sub cohort 2 | 124 | 62 | 50.0 | 133 | 29 | 21.8 | 28.20 | 16.66 | 39.10 |
| Immunogenicity cohort | 370 | 238 | 64.3 | 385 | 147 | 38.2 | 26.14 | 19.14 | 32.88 |

N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentration ≥ 20 U/ml
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

### 9.3.1.2. Antibody response to diphtheria toxoid and tetanus toxoid

**Table 31 Anti-Diphtheria and anti-Tetanus antibody GMC and seroprotection rates at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

| | | | | ≥ 0.1 IU/ml | | | | ≥ 1 IU/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| Anti-Diphtheria | HRV | PRE | 133 | 1 | 0.8 | 0.0 | 4.1 | 0 | 0.0 | 0.0 | 2.7 | 0.051 | 0.049 | 0.052 |
| | | VIS05 M 4 | 133 | 133 | 100 | 97.3 | 100 | 9 | 6.8 | 3.1 | 12.5 | 0.375 | 0.326 | 0.432 |
| | Placebo | PRE | 138 | 1 | 0.7 | 0.0 | 4.0 | 0 | 0.0 | 0.0 | 2.6 | 0.050 | 0.050 | 0.051 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 5 | 3.6 | 1.2 | 8.2 | 0.334 | 0.308 | 0.363 |
| Anti-Tetanus | HRV | PRE | 133 | 0 | 0.0 | 0.0 | 2.7 | 0 | 0.0 | 0.0 | 2.7 | 0.050 | 0.050 | 0.050 |
| | | VIS05 M 4 | 133 | 133 | 100 | 97.3 | 100 | 129 | 97.0 | 92.5 | 99.2 | 1.281 | 1.253 | 1.309 |
| | Placebo | PRE | 138 | 1 | 0.7 | 0.0 | 4.0 | 0 | 0.0 | 0.0 | 2.6 | 0.050 | 0.050 | 0.051 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 133 | 95.7 | 90.8 | 98.4 | 1.343 | 1.215 | 1.486 |

Seroprotection = Anti-Diphtheria and Anti-Tetanus antibody concentration ≥ 0.1 IU/mL
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

### 9.3.1.3. Antibody response to PT, FHA and PRN

**Table 32 Anti-PT, anti-FHA and anti-PRN antibody GMC and seropositivity rates at one month post dose 3 of DTPa of vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

| | | | | ≥ 5 EL.U/ml | | | | ≥ 20 EL.U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| **Antibody** | **Group** | **Timing** | **N** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** |
| Anti-PT | HRV | PRE | 131 | 43 | 32.8 | 24.9 | 41.6 | 1 | 0.8 | 0.0 | 4.2 | 3.4 | 3.1 | 3.7 |
| | | VIS05 M 4 | 133 | 133 | 100 | 97.3 | 100 | 133 | 100 | 97.3 | 100 | 88.9 | 84.9 | 93.2 |
| | Placebo | PRE | 139 | 34 | 24.5 | 17.6 | 32.5 | 0 | 0.0 | 0.0 | 2.6 | 3.2 | 3.0 | 3.4 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 139 | 100 | 97.4 | 100 | 90.5 | 86.4 | 94.8 |
| Anti-FHA | HRV | PRE | 131 | 31 | 23.7 | 16.7 | 31.9 | 0 | 0.0 | 0.0 | 2.8 | 3.1 | 2.9 | 3.3 |
| | | VIS05 M 4 | 133 | 133 | 100 | 97.3 | 100 | 132 | 99.2 | 95.9 | 100 | 59.5 | 55.8 | 63.5 |
| | Placebo | PRE | 139 | 47 | 33.8 | 26.0 | 42.3 | 1 | 0.7 | 0.0 | 3.9 | 3.5 | 3.2 | 3.8 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 139 | 100 | 97.4 | 100 | 65.8 | 61.3 | 70.5 |
| Anti-PRN | HRV | PRE | 131 | 3 | 2.3 | 0.5 | 6.5 | 0 | 0.0 | 0.0 | 2.8 | 2.6 | 2.5 | 2.6 |
| | | VIS05 M 4 | 133 | 133 | 100 | 97.3 | 100 | 131 | 98.5 | 94.7 | 99.8 | 41.9 | 37.6 | 46.5 |
| | Placebo | PRE | 139 | 5 | 3.6 | 1.2 | 8.2 | 0 | 0.0 | 0.0 | 2.6 | 2.6 | 2.5 | 2.7 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 139 | 100 | 97.4 | 100 | 50.8 | 44.3 | 58.1 |

GMC= geometric mean antibody concentration calculated for all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

## Table 33 Vaccine response for anti-PT and anti-FHA antibodies at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

| | | | | Vaccine response | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | |
| Antibody | Group | Pre-vacc status | N | n | % | LL | UL |
| Anti-PT | HRV | S- | 87 | 87 | 100 | 95.8 | 100 |
| | | S+ | 41 | 41 | 100 | 91.4 | 100 |
| | | Total | 128 | 128 | 100 | 97.2 | 100 |
| | Placebo | S- | 105 | 105 | 100 | 96.5 | 100 |
| | | S+ | 34 | 34 | 100 | 89.7 | 100 |
| | | Total | 139 | 139 | 100 | 97.4 | 100 |
| Anti-FHA | HRV | S- | 97 | 97 | 100 | 96.3 | 100 |
| | | S+ | 31 | 31 | 100 | 88.8 | 100 |
| | | Total | 128 | 128 | 100 | 97.2 | 100 |
| | Placebo | S- | 92 | 92 | 100 | 96.1 | 100 |
| | | S+ | 47 | 47 | 100 | 92.5 | 100 |
| | | Total | 139 | 139 | 100 | 97.4 | 100 |

S- = initially seronegative subjects (antibody concentrations < 5 EL.U/ml for anti-PT and anti-FHA) prior to vaccination
S+ = initially seropositive subjects (antibody concentrations ≥ 5 EL.U/ml for anti-PT and anti-FHA) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response is defined as:
Antibody concentration one month after third dose of vaccination ≥ 20 EL.U/ml
N = number of subjects with pre- and post-vaccination results available
n (%) = number (percentage) of responder
95% CI LL, UL = exact 95% confidence interval lower and upper limits

## Table 34 Vaccine response for Anti-PRN antibody at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)

| | | | Vaccine response | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| Group | Pre-vaccination status | N | n | % | LL | UL |
| HRV | S- | 125 | 123 | 98.4 | 94.3 | 99.8 |
| | S+ | 3 | 3 | 100 | 29.2 | 100 |
| | Total | 128 | 126 | 98.4 | 94.5 | 99.8 |
| Placebo | S- | 134 | 134 | 100 | 97.3 | 100 |
| | S+ | 5 | 4 | 80.0 | 28.4 | 99.5 |
| | Total | 139 | 138 | 99.3 | 96.1 | 100 |

S- = seronegative subjects (antibody concentration < 5 EL.U/ml for Anti-PRN) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 5 EL.U/ml for Anti-PRN) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as:
For initially seronegative subjects: post-vaccination antibody concentration ≥ 20 EL.U/ml (4-fold the assay cut-off)
For initially seropositive subjects: at least a 4-fold increase in antibody concentration from pre to post-vaccination concentration
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

### 9.3.1.4. Antibody response to poliovirus types 1, 2 and 3

**Table 35 Anti-Poliovirus 1, 2 and 3 antibody GMT and seroprotection rates at two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

| | | | | ≥ 8 $ED_{50}$ | | | | GMT | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| **Antibody** | **Group** | **Timing** | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** |
| Anti-Polio 1 | HRV | PRE | 136 | 63 | 46.3 | 37.7 | 55.1 | 8.9 | 7.5 | 10.5 |
| | | VIS05 M 4 | 136 | 136 | 100 | 97.3 | 100 | 2101.1 | 1734.8 | 2544.8 |
| | Placebo | PRE | 139 | 62 | 44.6 | 36.2 | 53.3 | 9.1 | 7.6 | 11.0 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 2259.4 | 1844.4 | 2767.9 |
| Anti-Polio 2 | HRV | PRE | 136 | 52 | 38.2 | 30.0 | 47.0 | 7.6 | 6.5 | 9.0 |
| | | VIS05 M 4 | 136 | 136 | 100 | 97.3 | 100 | 402.5 | 334.8 | 483.9 |
| | Placebo | PRE | 139 | 39 | 28.1 | 20.8 | 36.3 | 6.2 | 5.4 | 7.1 |
| | | VIS05 M 4 | 139 | 139 | 100 | 97.4 | 100 | 425.1 | 371.0 | 487.1 |
| Anti-Polio 3 | HRV | PRE | 136 | 32 | 23.5 | 16.7 | 31.6 | 5.6 | 4.9 | 6.3 |
| | | VIS05 M 4 | 136 | 135 | 99.3 | 96.0 | 100 | 426.6 | 342.7 | 531.0 |
| | Placebo | PRE | 139 | 29 | 20.9 | 14.4 | 28.6 | 5.7 | 4.9 | 6.6 |
| | | VIS05 M 4 | 139 | 138 | 99.3 | 96.1 | 100 | 360.3 | 303.0 | 428.3 |

Seroprotection = Anti-Poliovirus 1, 2, and 3 antibodies ≥ 8 $ED_{50}$
GMT = geometric mean titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody titres above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS05 M 4= Blood sample taken 2 months after dose 3 of OPV

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

**Table 36 Number and percentage of subjects reporting RVGE cases during the period between Visit 3 and Visit 6 classified by their anti-rotavirus IgA status at Visit 3 and Visit 6 (ATP cohort for efficacy)**

| | | HRV N = 27 | | Placebo N = 84 | |
|---|---|---|---|---|---|
| **Rotavirus IgA status at Visit 3** | **Rotavirus IgA status at Visit 6** | **n** | **%** | **n** | **%** |
| Positive | Negative | 1 | 20.0 | - | - |
| | Positive | 4 | 80.0 | - | - |
| | Unknown | 0 | 0.0 | - | - |
| Negative | Negative | 0 | 0.0 | 2 | 9.5 |
| | Positive | 3 | 100 | 19 | 90.5 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Unknown | Negative | 0 | 0.0 | 0 | 0.0 |
| | Positive | 0 | 0.0 | 0 | 0.0 |
| | Unknown | 19 | 100 | 63 | 100 |

N= Number of subjects reporting at least one RVGE event in each group
n= number of subjects reporting at least one RVGE event in the respective category
%= percentage of subjects in the respective category
Positive = Subjects with anti-RV IgA concentration above 20 U/ml
Negative = Subjects with anti-RV IgA concentration below 20 U/ml
Unknown= Subjects for whom anti-RV IgA concentration is not available or missing

## Table 37 Number and percentage of subjects reporting severe RVGE cases during the period between Visit 3 and Visit 6 classified by their anti-rotavirus IgA status at Visit 3 and Visit 6 (ATP cohort for efficacy)

| | | HRV N = 8 | | Placebo N = 31 | |
|---|---|---|---|---|---|
| **Rotavirus IgA status at Visit 3** | **Rotavirus IgA status at Visit 6** | **n** | **%** | **n** | **%** |
| Positive | Negative | 0 | 0.0 | - | - |
| | Positive | 1 | 100 | - | - |
| | Unknown | 0 | 0.0 | - | - |
| Negative | Negative | 0 | 0.0 | 0 | 0.0 |
| | Positive | 1 | 100 | 8 | 100 |
| | Unknown | 0 | 0.0 | 0 | 0.0 |
| Unknown | Negative | 0 | 0.0 | 0 | 0.0 |
| | Positive | 0 | 0.0 | 0 | 0.0 |
| | Unknown | 6 | 100 | 23 | 100 |

N= Number of subjects reporting at least one severe RVGE event in each group
n= number of subjects reporting at least one severe RVGE event in the respective category
%= percentage of subjects in the respective category
Positive = Subjects with anti-RV IgA concentration above 20 U/ml
Negative = Subjects with anti-RV IgA concentration below 20 U/ml
Unknown= Subjects for whom anti-RV IgA concentration is not available or missing

## Table 38 Number and percentage of subjects reporting RVGE cases from Visit 6 up to Visit 7 classified by their anti-rotavirus IgA status at Visit 6 (ATP cohort for efficacy for second year)

| | HRV N = 43 | | Placebo N = 78 | |
|---|---|---|---|---|
| **Rotavirus IgA status at Visit 6** | **n** | **%** | **n** | **%** |
| Negative | 7 | 16.3 | 17 | 21.8 |
| Positive | 11 | 25.6 | 1 | 1.3 |
| Unknown | 25 | 58.1 | 60 | 76.9 |

N= Number of subjects reporting at least one RVGE event in each group
n= number of subjects reporting at least one RVGE event in the respective category
%= percentage of subjects in the respective category
Positive = Subjects with anti-RV IgA concentration above 20 U/ml
Negative = Subjects with anti-RV IgA concentration below 20 U/ml
Unknown= Subjects for whom anti-RV IgA concentration is not available or missing

## Table 39 Number and percentage of subjects reporting severe RVGE cases from Visit 6 up to Visit 7 classified by their anti-rotavirus IgA status at Visit 6 (ATP cohort for efficacy for second year)

| | HRV N = 13 | | Placebo N = 43 | |
|---|---|---|---|---|
| **Rotavirus IgA status at Visit 6** | **n** | **%** | **n** | **%** |
| Negative | 2 | 15.4 | 8 | 18.6 |
| Positive | 2 | 15.4 | 1 | 2.3 |
| Unknown | 9 | 69.2 | 34 | 79.1 |

N= Number of subjects reporting at least one severe RVGE event in each group
n= number of subjects reporting at least one severe RVGE event in the respective category
%= percentage of subjects in the respective category
Positive = Subjects with anti-RV IgA concentration above 20 U/ml
Negative = Subjects with anti-RV IgA concentration below 20 U/ml
Unknown= Subjects for whom anti-RV IgA concentration is not available or missing

## Table 40 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-rotavirus IgA antibody status at Visit 3** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| Negative | HRV | 115 | 8 | 7.0 | 3.1 | 13.2 | 34.1 | -42.7 | 73.4 | 0.3636 |
| | Placebo | 379 | 40 | 10.6 | 7.6 | 14.1 | - | - | - | - |
| Positive | HRV | 301 | 17 | 5.6 | 3.3 | 8.9 | -86.4 | -7689.1 | 70.8 | 0.9142 |
| | Placebo | 33 | 1 | 3.0 | 0.1 | 15.8 | - | - | - | - |
| Unknown | HRV | 1159 | 45 | 3.9 | 2.8 | 5.2 | 64.2 | 49.3 | 75.1 | <0.0001 |
| | Placebo | 1161 | 126 | 10.9 | 9.1 | 12.8 | - | - | - | - |

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 3
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 41 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-rotavirus IgA antibody status at Visit 3** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| Negative | HRV | 115 | 3 | 2.6 | 0.5 | 7.4 | 45.1 | -88.2 | 89.6 | 0.4891 |
| | Placebo | 379 | 18 | 4.7 | 2.8 | 7.4 | - | - | - | - |
| Positive | HRV | 301 | 3 | 1.0 | 0.2 | 2.9 | Und. | Und. | Und. | 1.0000 |
| | Placebo | 33 | 0 | 0.0 | 0.0 | 10.6 | - | - | - | - |
| Unknown | HRV | 1159 | 15 | 1.3 | 0.7 | 2.1 | 73.6 | 52.8 | 86.1 | <0.0001 |
| | Placebo | 1161 | 57 | 4.9 | 3.7 | 6.3 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode, by status of anti-rotavirus IgA antibodies concentrations at Visit 3
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Und. = cannot be estimated

## Table 42 Percentage of subjects reporting RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-rotavirus IgA antibody status at Visit 3** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| Negative | HRV | 115 | 3 | 2.6 | 0.5 | 7.4 | 55.1 | -49.6 | 91.4 | 0.2666 |
| | Placebo | 379 | 22 | 5.8 | 3.7 | 8.7 | - | - | - | - |
| Positive | HRV | 301 | 5 | 1.7 | 0.5 | 3.8 | 45.2 | -2492.7 | 93.9 | 0.9286 |
| | Placebo | 33 | 1 | 3.0 | 0.1 | 15.8 | - | - | - | - |
| Unknown | HRV | 1159 | 19 | 1.6 | 1.0 | 2.5 | 71.6 | 52.1 | 83.9 | <0.0001 |
| | Placebo | 1161 | 67 | 5.8 | 4.5 | 7.3 | - | - | - | - |

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 3
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 43 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-rotavirus IgA antibody status at Visit 3** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| Negative | HRV | 115 | 1 | 0.9 | 0.0 | 4.7 | 63.4 | -164.3 | 99.2 | 0.5701 |
| | Placebo | 379 | 9 | 2.4 | 1.1 | 4.5 | - | - | - | - |
| Positive | HRV | 301 | 1 | 0.3 | 0.0 | 1.8 | Und. | Und. | Und. | 1.0000 |
| | Placebo | 33 | 0 | 0.0 | 0.0 | 10.6 | - | - | - | - |
| Unknown | HRV | 1159 | 6 | 0.5 | 0.2 | 1.1 | 73.9 | 34.0 | 91.3 | 0.0024 |
| | Placebo | 1161 | 23 | 2.0 | 1.3 | 3.0 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode, by status of anti-rotavirus IgA antibodies concentrations at Visit 3
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Und. = cannot be estimated

## Table 44 Percentage of subjects reporting RV GE episode and efficacy of the vaccine from Visit 6 to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 6 (ATP cohort for efficacy for second year follow up)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-rotavirus IgA antibody status at Visit 6** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| Negative | HRV | 132 | 7 | 5.3 | 2.2 | 10.6 | 26.4 | -86.8 | 74.2 | 0.6496 |
| | Placebo | 236 | 17 | 7.2 | 4.3 | 11.3 | - | - | - | - |
| Positive | HRV | 252 | 11 | 4.4 | 2.2 | 7.7 | -572.2 | -28834.6 | 2.3 | 0.0545 |
| | Placebo | 154 | 1 | 0.6 | 0.0 | 3.6 | - | - | - | - |
| Unknown | HRV | 1116 | 25 | 2.2 | 1.5 | 3.3 | 59.3 | 34.2 | 75.6 | 0.0001 |
| | Placebo | 1089 | 60 | 5.5 | 4.2 | 7.0 | - | - | - | - |

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 6
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 45 Percentage of subjects reporting severe RV GE episode and efficacy of the vaccine from Visit 6 to Visit 7 by status of anti-rotavirus IgA antibody concentration at Visit 6 (ATP cohort for efficacy for second year)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Anti-rotavirus IgA antibody status at Visit 6** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| Negative | HRV | 132 | 2 | 1.5 | 0.2 | 5.4 | 55.3 | -124.0 | 95.4 | 0.4864 |
| | Placebo | 236 | 8 | 3.4 | 1.5 | 6.6 | - | - | - | - |
| Positive | HRV | 252 | 2 | 0.8 | 0.1 | 2.8 | -22.2 | -7110.8 | 93.6 | 1.0000 |
| | Placebo | 154 | 1 | 0.6 | 0.0 | 3.6 | - | - | - | - |
| Unknown | HRV | 1116 | 9 | 0.8 | 0.4 | 1.5 | 74.2 | 45.0 | 89.1 | 0.0001 |
| | Placebo | 1089 | 34 | 3.1 | 2.2 | 4.3 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one severe RV GE episode, by status of anti-rotavirus IgA antibodies concentrations at Visit 6
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 1 Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 (ATP cohort for immunogenicity - sub cohort 1)**

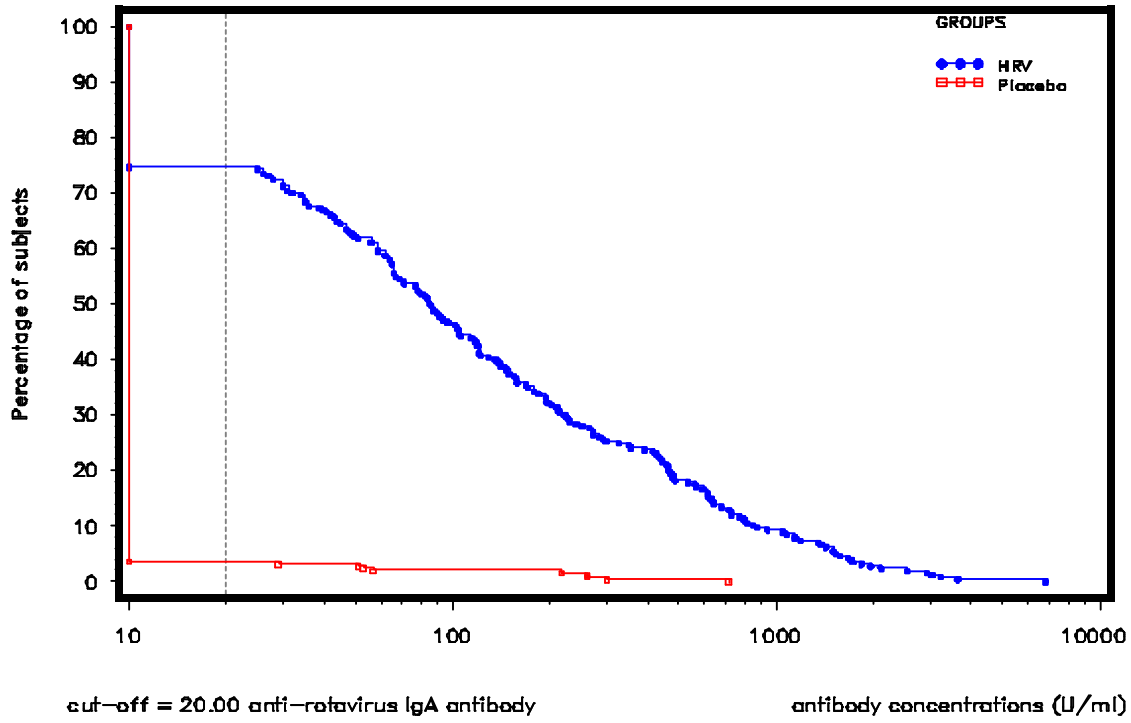


**Figure 2** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 (ATP cohort for immunogenicity (sub cohort 2) – anti-RV IgA)**

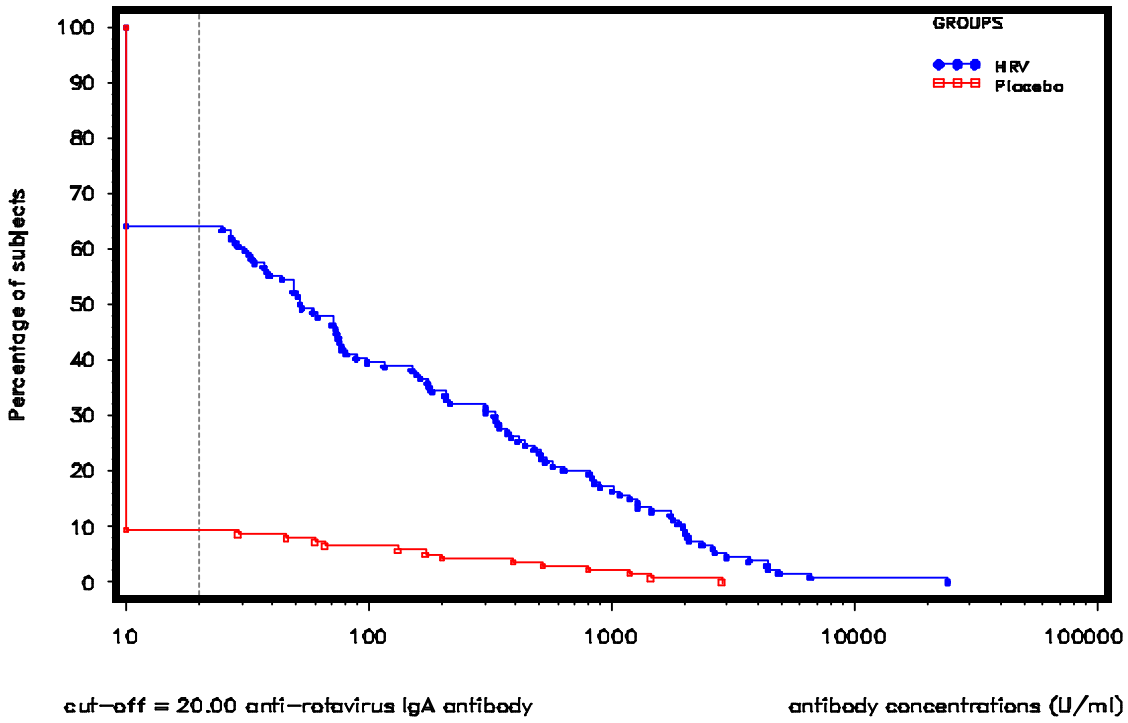


**Figure 3** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 (ATP cohort for immunogenicity)**

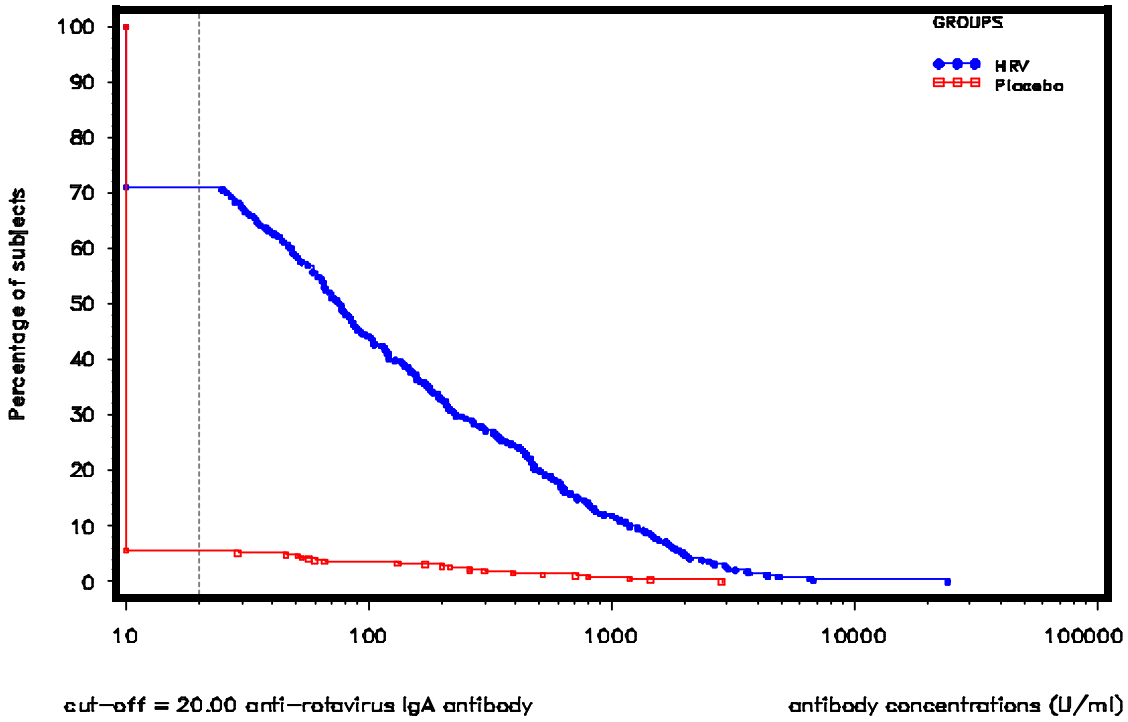


**Figure 4** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 6 (ATP cohort for immunogenicity)**

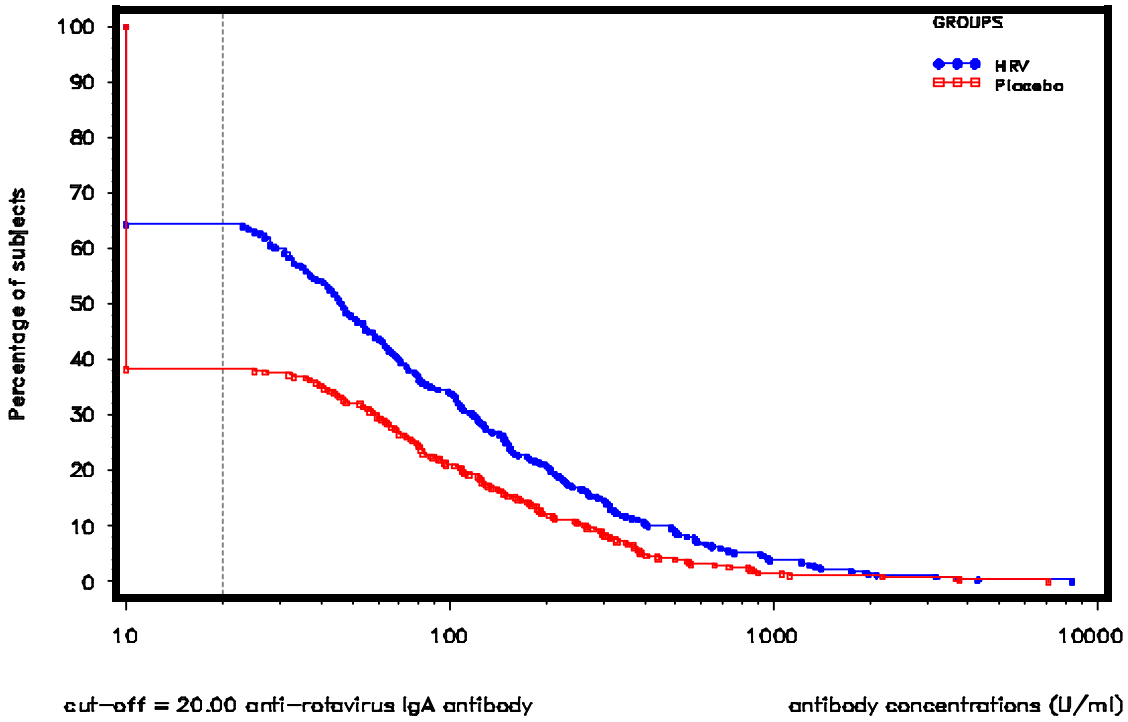


**Figure 5** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 6 (ATP cohort for immunogenicity - sub cohort 1)**

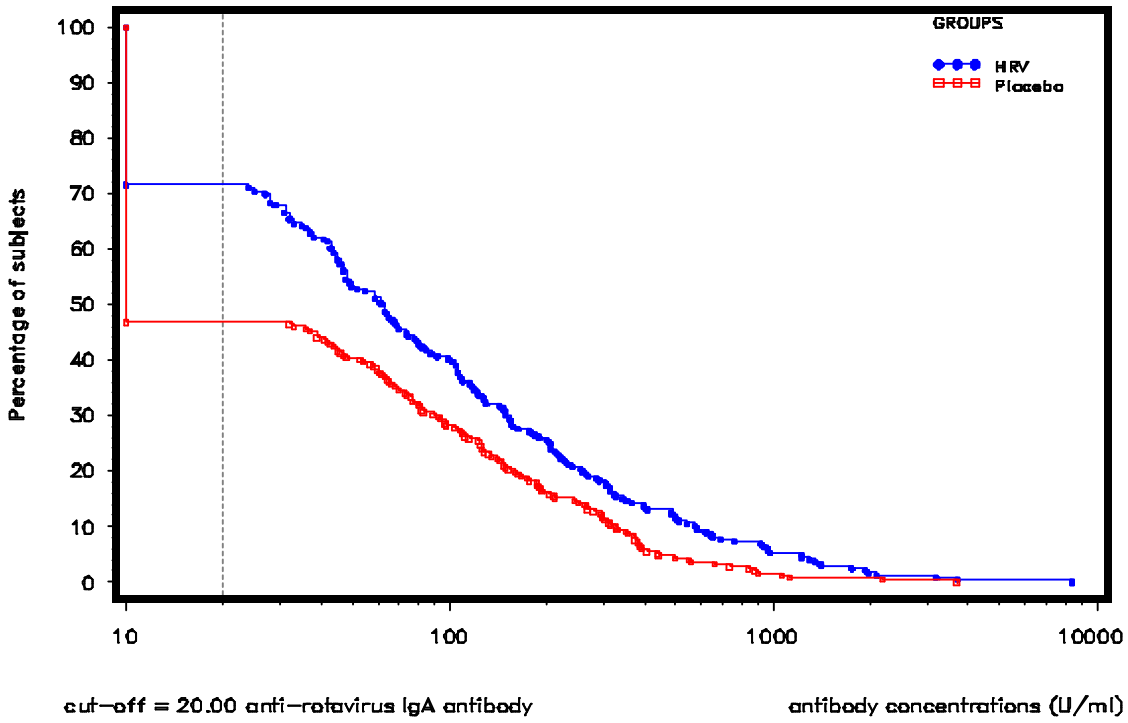


**Figure 6** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 6 (ATP cohort for immunogenicity(sub cohort 2) – anti-RV IgA)**

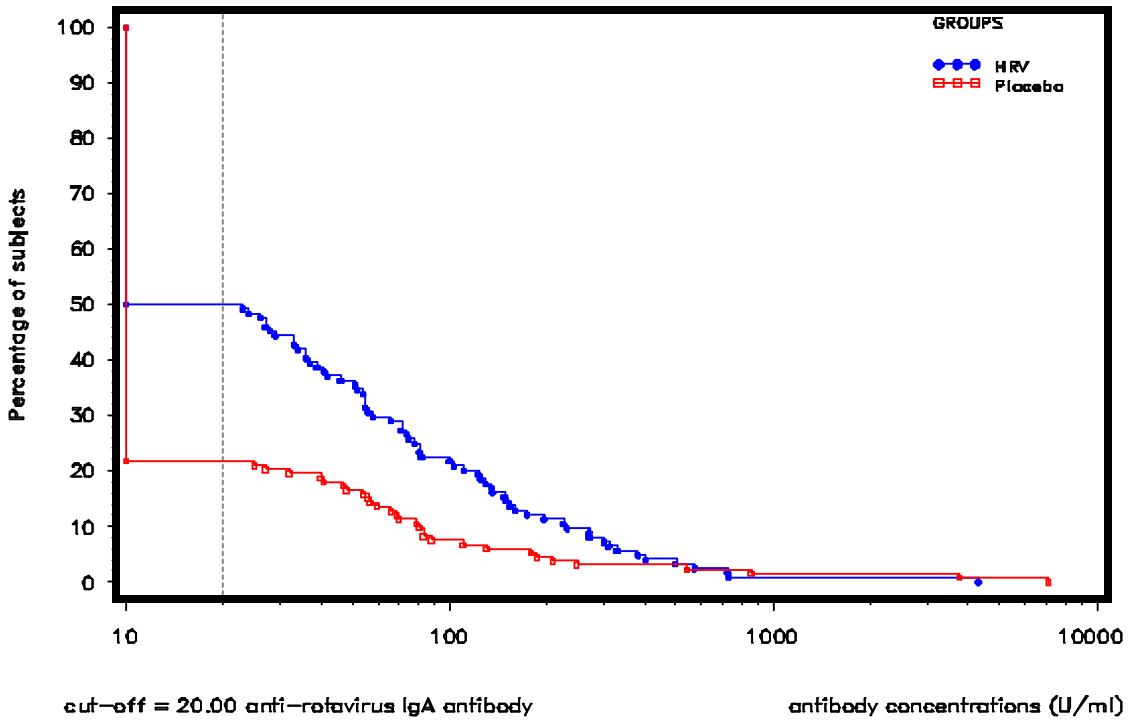


**Figure 7** **Reverse cumulative curves for anti-diphtheria antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

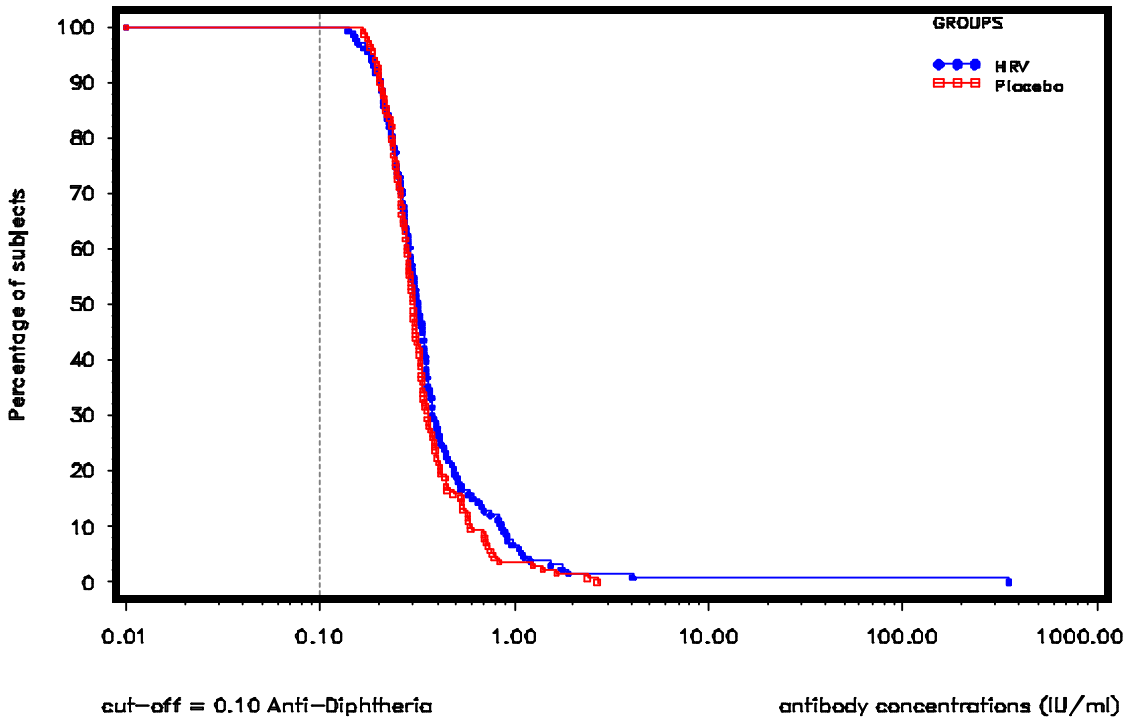


**Figure 8** **Reverse cumulative curves for anti-tetanus antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

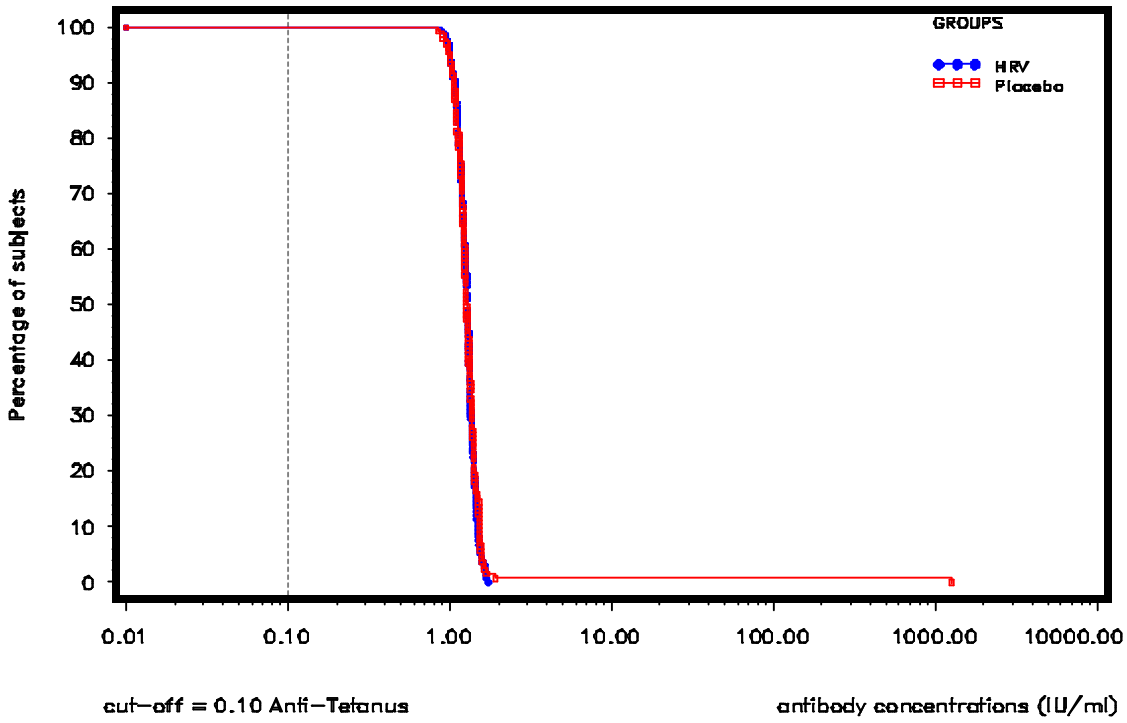


**Figure 9** **Reverse cumulative curves for anti-polio 1 antibody titres at two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

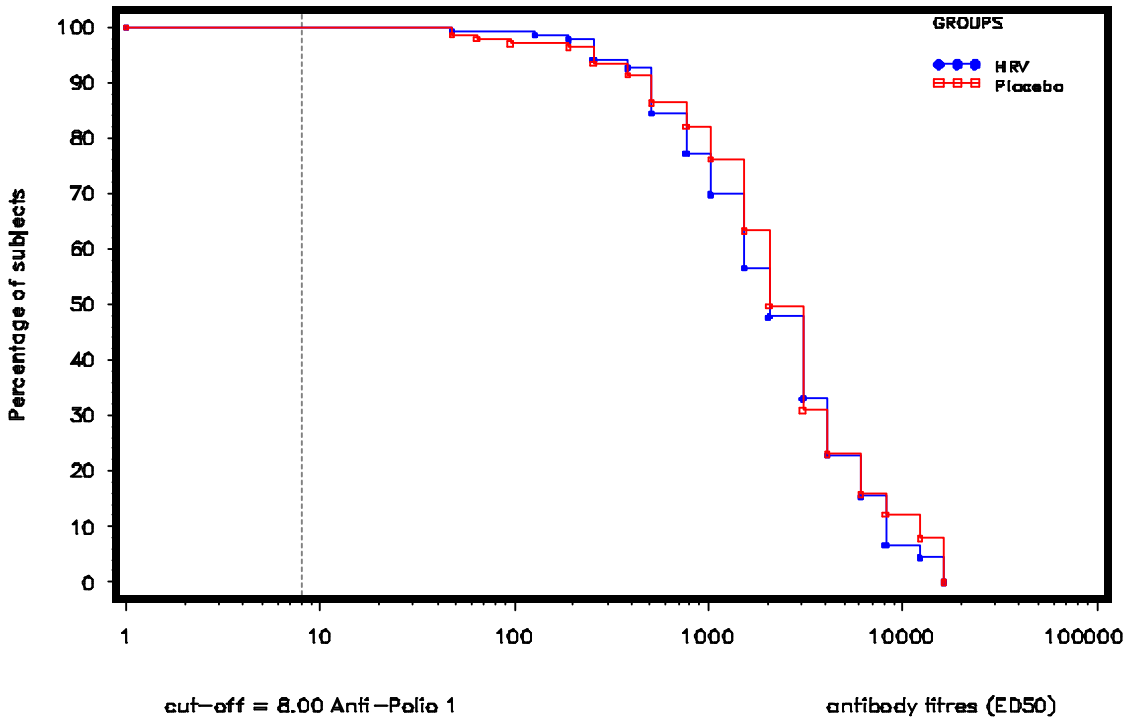


**Figure 10** **Reverse cumulative curves for anti-polio 2 antibody titres two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

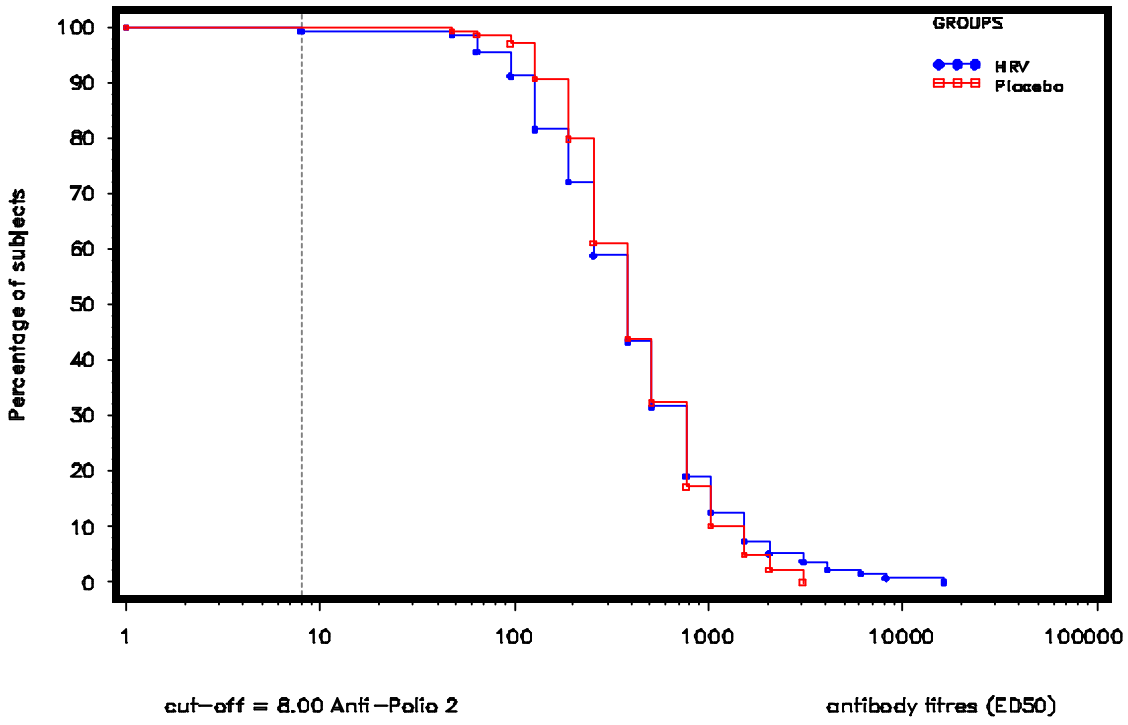


**Figure 11** **Reverse cumulative curves for anti-polio 3 antibody titres two months post dose 3 of OPV vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

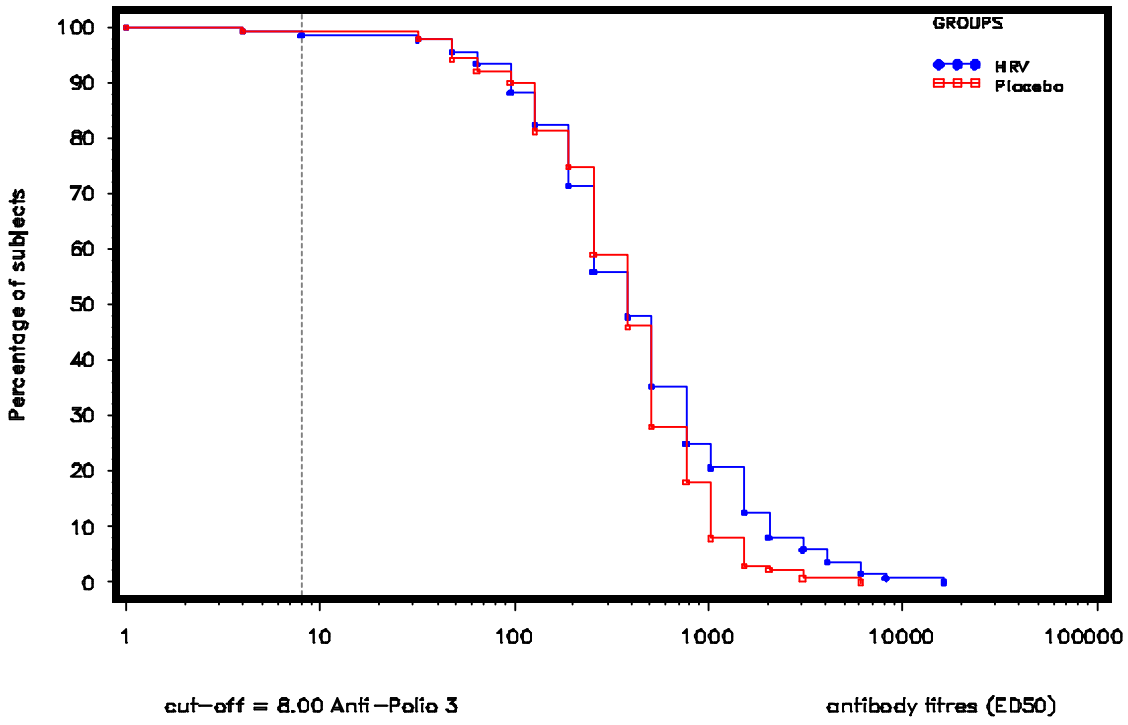


**Figure 12** **Reverse cumulative curves for anti-FHA antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

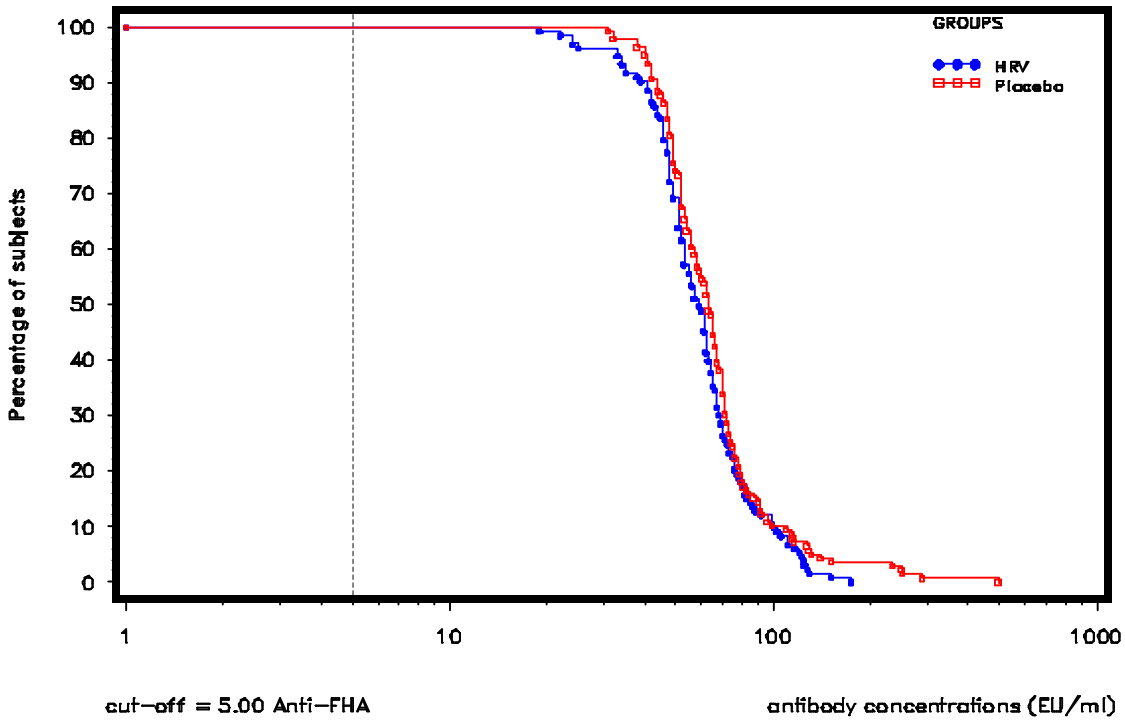


**Figure 13** **Reverse cumulative curves for anti-PT antibody concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**

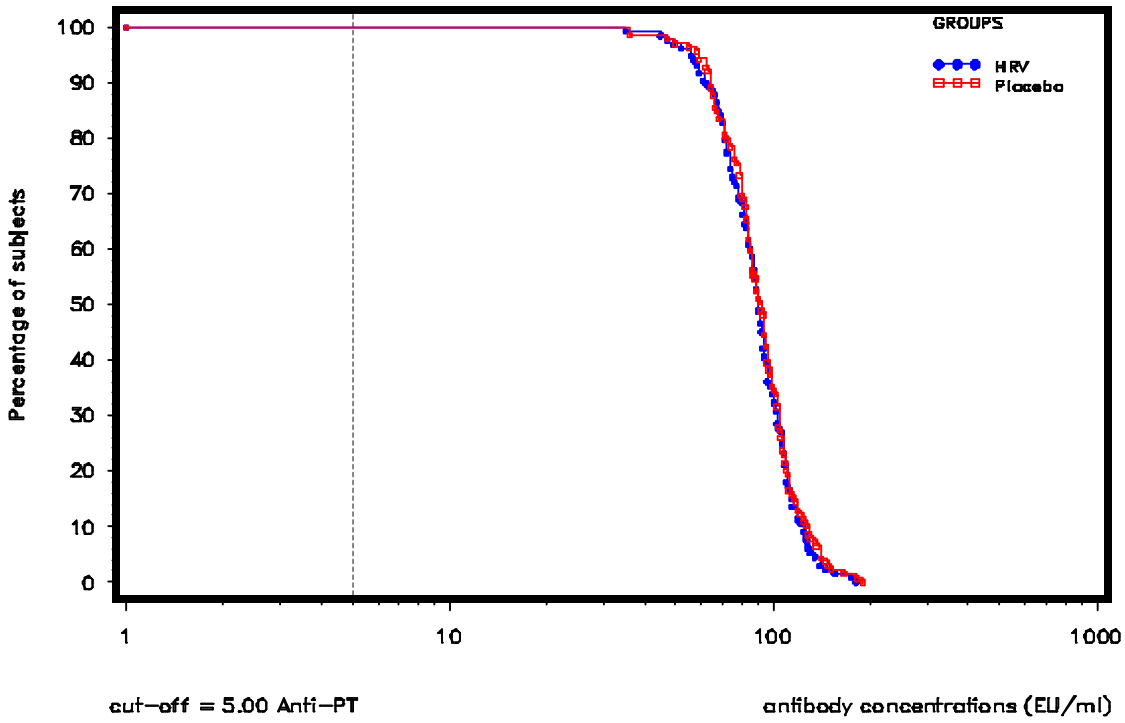
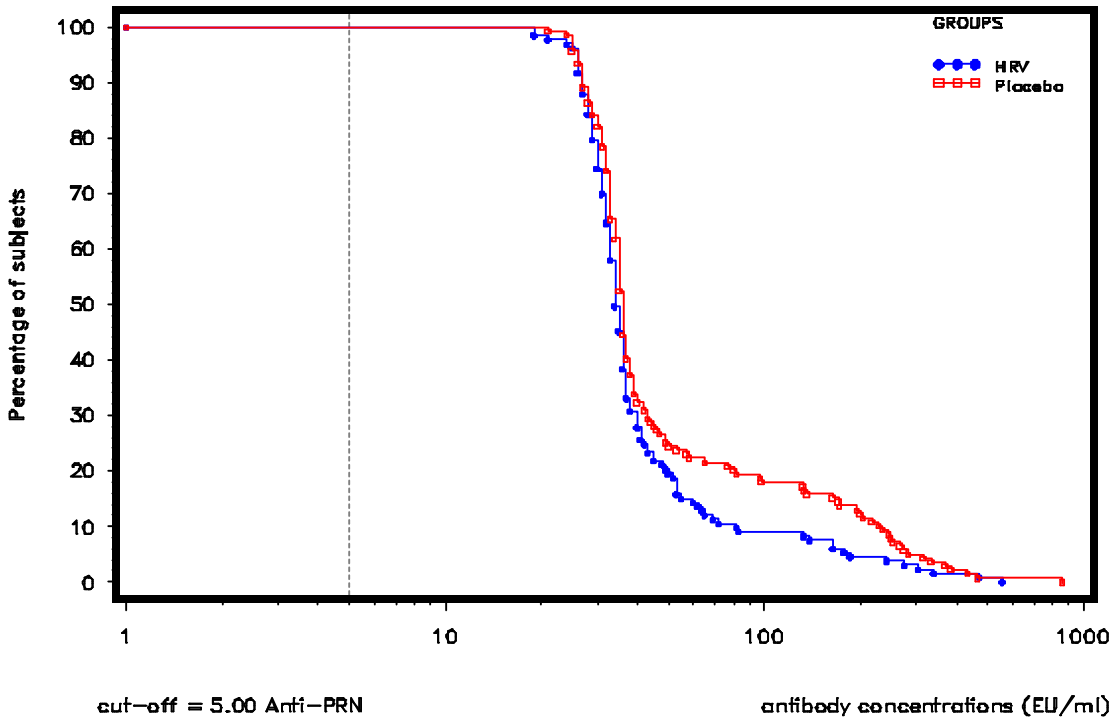


**Figure 14** **Reverse cumulative curves for anti PRN concentrations at one month post dose 3 of DTPa vaccine (ATP cohort for immunogenicity (sub cohort 2) – co-administered vaccination)**



## 9.3.2. Total vaccinated cohort analysis

### 9.3.2.1. Anti-rotavirus IgA antibody response

**Table 46 Anti-rotavirus IgA antibody GMC and seropositivity rates at Visit 3 and at Visit 6 (Total vaccinated cohort – Immunogenicity cohort)**

| | | | | ≥ 20 U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Cohort | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| Immunogenicity sub cohort 1 | HRV | PRE | 306 | 6 | 2.0 | 0.7 | 4.2 | <20.0 | - | - |
| | | VIS03 M 2 | 277 | 209 | 75.5 | 69.9 | 80.4 | 97.4 | 79.5 | 119.4 |
| | | VIS06 M 12 | 270 | 198 | 73.3 | 67.6 | 78.5 | 69.9 | 58.1 | 84.1 |
| | Placebo | PRE | 305 | 10 | 3.3 | 1.6 | 5.9 | <20.0 | - | - |
| | | VIS03 M 2 | 277 | 18 | 6.5 | 3.9 | 10.1 | <20.0 | - | - |
| | | VIS06 M 12 | 280 | 137 | 48.9 | 42.9 | 54.9 | 38.3 | 31.9 | 45.9 |
| Immunogenicity sub cohort 2 | HRV | PRE | 153 | 4 | 2.6 | 0.7 | 6.6 | <20.0 | - | - |
| | | VIS03 M 2 | 147 | 97 | 66.0 | 57.7 | 73.6 | 90.1 | 64.5 | 125.8 |
| | | VIS06 M 12 | 138 | 72 | 52.2 | 43.5 | 60.7 | 33.6 | 26.5 | 42.6 |
| | Placebo | PRE | 152 | 2 | 1.3 | 0.2 | 4.7 | <20.0 | - | - |
| | | VIS03 M 2 | 149 | 17 | 11.4 | 6.8 | 17.6 | <20.0 | - | - |
| | | VIS06 M 12 | 144 | 35 | 24.3 | 17.6 | 32.1 | <20.0 | - | - |
| Immunogenicity cohort | HRV | PRE | 459 | 10 | 2.2 | 1.0 | 4.0 | <20.0 | - | - |
| | | VIS03 M 2 | 424 | 306 | 72.2 | 67.6 | 76.4 | 94.8 | 79.6 | 113.0 |
| | | VIS06 M 12 | 408 | 270 | 66.2 | 61.4 | 70.8 | 54.6 | 47.0 | 63.4 |
| | Placebo | PRE | 457 | 12 | 2.6 | 1.4 | 4.5 | <20.0 | - | - |
| | | VIS03 M 2 | 426 | 35 | 8.2 | 5.8 | 11.2 | <20.0 | - | - |
| | | VIS06 M 12 | 424 | 172 | 40.6 | 35.9 | 45.4 | 30.0 | 26.0 | 34.6 |

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2
VIS06 M 12= Blood sample taken at year 1 of age
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

**Table 47 Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies at Visit 3 and at Visit 6 (Total vaccinated cohort – Immunogenicity cohort)**

| | | | | GMC | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| **Cohort** | **Group** | **Timing** | **N** | **value** | **LL** | **UL** |
| Immunogenicity sub cohort 1 | HRV | PRE | 6 | 260.7 | 53.1 | 1280.5 |
| | | VIS03 M 2 | 209 | 204.4 | 171.2 | 243.9 |
| | | VIS06 M 12 | 198 | 141.7 | 120.4 | 166.9 |
| | Placebo | PRE | 10 | 184.1 | 62.3 | 543.6 |
| | | VIS03 M 2 | 18 | 156.0 | 87.1 | 279.4 |
| | | VIS06 M 12 | 137 | 155.4 | 131.0 | 184.3 |
| Immunogenicity sub cohort 1 | HRV | PRE | 4 | 762.6 | 31.5 | 18435.8 |
| | | VIS03 M 2 | 97 | 279.8 | 202.8 | 386.1 |
| | | VIS06 M 12 | 72 | 102.1 | 78.5 | 132.7 |
| | Placebo | PRE | 2 | 2193.9 | 0.0 | 1.2622E8 |
| | | VIS03 M 2 | 17 | 370.2 | 172.3 | 795.3 |
| | | VIS06 M 12 | 35 | 128.6 | 82.1 | 201.3 |
| Immunogenicity cohort | HRV | PRE | 10 | 400.5 | 117.9 | 1360.1 |
| | | VIS03 M 2 | 306 | 225.8 | 192.8 | 264.4 |
| | | VIS06 M 12 | 270 | 129.9 | 113.0 | 149.2 |
| | Placebo | PRE | 12 | 278.2 | 93.6 | 827.1 |
| | | VIS03 M 2 | 35 | 237.3 | 147.4 | 382.0 |
| | | VIS06 M 12 | 172 | 149.5 | 127.2 | 175.8 |

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
PRE= Blood sample taken prior to dose 1
VIS03 M 2= Blood sample taken 1 month after dose 2
VIS06 M 12= Blood sample taken at year 1 of age
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

## Table 48 Anti-rotavirus IgA antibody GMC and seropositivity rates at Visit 6 excluding subjects who had RVGE between Visit 1 and Visit 6 (Total vaccinated cohort – Immunogenicity cohort)

| | | | | ≥ 20 U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Cohort | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| Immunogenicity sub cohort 1 | HRV | VIS06 M 12 | 262 | 191 | 72.9 | 67.1 | 78.2 | 68.5 | 56.8 | 82.6 |
| | Placebo | VIS06 M 12 | 262 | 121 | 46.2 | 40.0 | 52.4 | 34.9 | 29.0 | 42.0 |
| Immunogenicity sub cohort 2 | HRV | VIS06 M 12 | 137 | 71 | 51.8 | 43.1 | 60.4 | 33.4 | 26.3 | 42.5 |
| | Placebo | VIS06 M 12 | 138 | 29 | 21.0 | 14.5 | 28.8 | <20.0 | - | - |
| Immunogenicity cohort | HRV | VIS06 M 12 | 399 | 262 | 65.7 | 60.8 | 70.3 | 53.6 | 46.1 | 62.3 |
| | Placebo | VIS06 M 12 | 400 | 150 | 37.5 | 32.7 | 42.4 | 27.3 | 23.7 | 31.6 |

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
VIS06 M 12= Blood sample taken at year 1 of age
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

## Table 49 Percentage of subjects with antiviral medication from dose 1 till Visit 3 (Total vaccinated cohort – Immunogenicity cohort)

| | | HRV N = 459 | | Placebo N = 459 | |
|---|---|---|---|---|---|
| Medication | Parameters or Categories | n | % | n | % |
| Antiviral received | No | 436 | 95.0 | 431 | 93.9 |
| | Yes | 23 | 5.0 | 28 | 6.1 |

N = number of subjects in a given group
n/% = number / percentage of subjects antiviral received or not

## Table 50 Anti-rotavirus IgA antibody GMC and seropositivity rate at Visit 3 by antiviral medication status (Total vaccinated cohort – Immunogenicity cohort)

| | | | | ≥ 20 U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| Medication | Group | Timing | N | n | % | LL | UL | value | LL | UL |
| Antiviral received | HRV | PRE | 23 | 0 | 0.0 | 0.0 | 14.8 | <20.0 | - | - |
| | | VIS03 M 2 | 23 | 14 | 60.9 | 38.5 | 80.3 | 88.2 | 36.3 | 214.3 |
| | Placebo | PRE | 28 | 0 | 0.0 | 0.0 | 12.3 | <20.0 | - | - |
| | | VIS03 M 2 | 28 | 3 | 10.7 | 2.3 | 28.2 | <20.0 | - | - |
| Antiviral not received | HRV | PRE | 436 | 10 | 2.3 | 1.1 | 4.2 | <20.0 | - | - |
| | | VIS03 M 2 | 401 | 292 | 72.8 | 68.2 | 77.1 | 95.2 | 79.6 | 113.9 |
| | Placebo | PRE | 429 | 12 | 2.8 | 1.5 | 4.8 | <20.0 | - | - |
| | | VIS03 M 2 | 398 | 32 | 8.0 | 5.6 | 11.2 | <20.0 | - | - |

GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
VIS03 M 2= Blood sample taken 1 month after dose 2

## Table 51 Difference between groups in percentage of subjects who were seropositive at Visit 3 for serum anti-rotavirus IgA antibody (Total vaccinated cohort – Immunogenicity cohort)

| Cohort | | | | | | | Difference in seropositive rate (HRV minus Placebo) | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV | | | Placebo | | | | 95% CI | |
| | N | n | % | N | n | % | % | LL | UL |
| Immunogenicity sub cohort 1 | 277 | 209 | 75.5 | 277 | 18 | 6.5 | 68.95 | 62.70 | 74.38 |
| Immunogenicity sub cohort 2 | 147 | 97 | 66.0 | 149 | 17 | 11.4 | 54.58 | 44.80 | 63.17 |
| Immunogenicity cohort | 426 | 307 | 72.2 | 426 | 35 | 8.2 | 63.95 | 58.71 | 68.70 |

N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentration ≥ 20 U/ml
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

## Table 52 Difference between groups in percentage of subjects who were seropositive at Visit 6 for anti-rotavirus IgA antibody (Total vaccinated cohort – Immunogenicity cohort)

| Cohort | | | | | | | Difference in seropositive rate (HRV minus Placebo) | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV | | | Placebo | | | | 95% CI | |
| | N | n | % | N | n | % | % | LL | UL |
| Immunogenicity sub cohort 1 | 270 | 198 | 73.3 | 280 | 137 | 48.9 | 24.40 | 16.38 | 32.12 |
| Immunogenicity sub cohort 2 | 138 | 72 | 52.2 | 144 | 35 | 24.3 | 27.87 | 16.70 | 38.40 |
| Immunogenicity cohort | 408 | 270 | 66.2 | 424 | 172 | 40.6 | 25.61 | 18.95 | 32.03 |

N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentration ≥ 20 U/ml
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit
Immunogenicity cohort = Immunogenicity sub cohort 1 + Immunogenicity sub cohort 2

### 9.3.2.2. Antibody response to diphtheria toxoid and tetanus toxoid

**Table 53 Anti-Diphtheria and anti-Tetanus antibody GMC and seroprotection rates at one month post dose 3 of DTPa vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)**

| | | | | ≥ 0.1 IU/ml | | | | ≥ 1 IU/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| Anti-Diphtheria | HRV | PRE | 150 | 2 | 1.3 | 0.2 | 4.7 | 0 | 0.0 | 0.0 | 2.4 | 0.051 | 0.050 | 0.053 |
| | | VIS05 M 4 | 143 | 143 | 100 | 97.5 | 100 | 9 | 6.3 | 2.9 | 11.6 | 0.371 | 0.325 | 0.424 |
| | Placebo | PRE | 152 | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 | 0.050 | 0.050 | 0.051 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 5 | 3.4 | 1.1 | 7.7 | 0.333 | 0.308 | 0.359 |
| Anti-Tetanus | HRV | PRE | 150 | 0 | 0.0 | 0.0 | 2.4 | 0 | 0.0 | 0.0 | 2.4 | 0.050 | 0.050 | 0.050 |
| | | VIS05 M 4 | 143 | 143 | 100 | 97.5 | 100 | 138 | 96.5 | 92.0 | 98.9 | 1.278 | 1.250 | 1.306 |
| | Placebo | PRE | 152 | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 | 0.050 | 0.050 | 0.051 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 141 | 95.3 | 90.5 | 98.1 | 1.327 | 1.207 | 1.459 |

Seroprotection = Anti-Diphtheria and Anti-Tetanus antibody concentration ≥ 0.1 IU/mL
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

### 9.3.2.3. Antibody response to PT, FHA and PRN

**Table 54 Anti-PT, anti-FHA and anti-PRN antibody GMC and seropositivity rates at one month post dose 3 of DTPa of vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)**

| | | | | ≥ 5 EL.U/ml | | | | ≥ 20 EL.U/ml | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | | 95% CI | | | 95% CI | |
| Antibody | Group | Timing | N | n | % | LL | UL | n | % | LL | UL | value | LL | UL |
| Anti-PT | HRV | PRE | 148 | 51 | 34.5 | 26.8 | 42.7 | 2 | 1.4 | 0.2 | 4.8 | 3.5 | 3.2 | 3.8 |
| | | VIS05 M 4 | 143 | 143 | 100 | 97.5 | 100 | 143 | 100 | 97.5 | 100 | 88.7 | 84.9 | 92.7 |
| | Placebo | PRE | 153 | 38 | 24.8 | 18.2 | 32.5 | 1 | 0.7 | 0.0 | 3.6 | 3.2 | 3.0 | 3.5 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 148 | 100 | 97.5 | 100 | 89.5 | 85.6 | 93.7 |
| Anti-FHA | HRV | PRE | 148 | 38 | 25.7 | 18.9 | 33.5 | 0 | 0.0 | 0.0 | 2.5 | 3.2 | 3.0 | 3.4 |
| | | VIS05 M 4 | 143 | 143 | 100 | 97.5 | 100 | 142 | 99.3 | 96.2 | 100 | 59.6 | 56.0 | 63.4 |
| | Placebo | PRE | 153 | 49 | 32.0 | 24.7 | 40.0 | 1 | 0.7 | 0.0 | 3.6 | 3.4 | 3.2 | 3.7 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 148 | 100 | 97.5 | 100 | 65.0 | 60.8 | 69.5 |
| Anti-PRN | HRV | PRE | 148 | 5 | 3.4 | 1.1 | 7.7 | 0 | 0.0 | 0.0 | 2.5 | 2.6 | 2.5 | 2.7 |
| | | VIS05 M 4 | 143 | 143 | 100 | 97.5 | 100 | 141 | 98.6 | 95.0 | 99.8 | 42.7 | 38.3 | 47.7 |
| | Placebo | PRE | 153 | 5 | 3.3 | 1.1 | 7.5 | 0 | 0.0 | 0.0 | 2.4 | 2.6 | 2.5 | 2.6 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 148 | 100 | 97.5 | 100 | 50.1 | 43.9 | 57.1 |

GMC= geometric mean antibody concentration calculated for all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody concentrations above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

## Table 55 Vaccine response for anti-PT and anti-FHA antibodies at one month post dose 3 of DTPa vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

| | | | | Vaccine response | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | |
| **Antibody** | **Group** | **Pre-vacc status** | **N** | **n** | **%** | **LL** | **UL** |
| Anti-PT | HRV | S- | 92 | 92 | 100 | 96.1 | 100 |
| | | S+ | 46 | 46 | 100 | 92.3 | 100 |
| | | Total | 138 | 138 | 100 | 97.4 | 100 |
| | Placebo | S- | 112 | 112 | 100 | 96.8 | 100 |
| | | S+ | 36 | 36 | 100 | 90.3 | 100 |
| | | Total | 148 | 148 | 100 | 97.5 | 100 |
| Anti-FHA | HRV | S- | 103 | 103 | 100 | 96.5 | 100 |
| | | S+ | 35 | 35 | 100 | 90.0 | 100 |
| | | Total | 138 | 138 | 100 | 97.4 | 100 |
| | Placebo | S- | 101 | 101 | 100 | 96.4 | 100 |
| | | S+ | 47 | 47 | 100 | 92.5 | 100 |
| | | Total | 148 | 148 | 100 | 97.5 | 100 |

S- = initially seronegative subjects (antibody concentrations < 5 EL.U/ml for anti-PT and anti-FHA) prior to vaccination
S+ = initially seropositive subjects (antibody concentrations ≥ 5 EL.U/ml for anti-PT and anti-FHA) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response is defined as:
Antibody concentration one month after third dose of vaccination ≥ 20 EL.U/ml
N = number of subjects with pre- and post-vaccination results available
n (%) = number (percentage) of responder
95% CI LL, UL = exact 95% confidence interval lower and upper limits

## Table 56 Vaccine response for Anti-PRN antibody at one month post dose 3 of DTPa vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)

| | | | Vaccine response | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| **Group** | **Pre-vaccination status** | **N** | **n** | **%** | **LL** | **UL** |
| HRV | S- | 135 | 133 | 98.5 | 94.8 | 99.8 |
| | S+ | 3 | 3 | 100 | 29.2 | 100 |
| | Total | 138 | 136 | 98.6 | 94.9 | 99.8 |
| Placebo | S- | 143 | 143 | 100 | 97.5 | 100 |
| | S+ | 5 | 4 | 80.0 | 28.4 | 99.5 |
| | Total | 148 | 147 | 99.3 | 96.3 | 100 |

S- = seronegative subjects (antibody concentration < 5 EL.U/ml for Anti-PRN) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 5 EL.U/ml for Anti-PRN) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as :
For initially seronegative subjects: post-vaccination antibody concentration ≥ 20 EL.U/ml (4-fold the assay cut-off)
For initially seropositive subjects: at least a 4-fold increase in antibody concentration from pre to post-vaccination
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

### 9.3.2.4. Antibody response to poliovirus types 1, 2 and 3

**Table 57 Anti-Poliovirus 1, 2 and 3 antibody GMT and seroprotection rates at two months post dose 3 of OPV vaccine (Total vaccinated cohort – Immunogenicity sub cohort 2)**

| | | | | ≥ 8 $ED_{50}$ | | | | GMT | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | |
| **Antibody** | **Group** | **Timing** | **N** | **n** | **%** | **LL** | **UL** | **value** | **LL** | **UL** |
| Anti-Polio 1 | HRV | PRE | 153 | 72 | 47.1 | 38.9 | 55.3 | 9.1 | 7.7 | 10.8 |
| | | VIS05 M 4 | 147 | 147 | 100 | 97.5 | 100 | 2066.9 | 1723.3 | 2479.1 |
| | Placebo | PRE | 153 | 65 | 42.5 | 34.5 | 50.7 | 8.7 | 7.3 | 10.3 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 2258.3 | 1843.7 | 2766.2 |
| Anti-Polio 2 | HRV | PRE | 153 | 60 | 39.2 | 31.4 | 47.4 | 7.7 | 6.6 | 8.9 |
| | | VIS05 M 4 | 147 | 147 | 100 | 97.5 | 100 | 392.6 | 330.4 | 466.6 |
| | Placebo | PRE | 153 | 44 | 28.8 | 21.7 | 36.6 | 6.3 | 5.5 | 7.2 |
| | | VIS05 M 4 | 148 | 148 | 100 | 97.5 | 100 | 443.2 | 386.6 | 508.2 |
| Anti-Polio 3 | HRV | PRE | 153 | 38 | 24.8 | 18.2 | 32.5 | 5.6 | 5.0 | 6.3 |
| | | VIS05 M 4 | 147 | 146 | 99.3 | 96.3 | 100 | 429.9 | 349.2 | 529.4 |
| | Placebo | PRE | 153 | 32 | 20.9 | 14.8 | 28.2 | 5.7 | 5.0 | 6.5 |
| | | VIS05 M 4 | 148 | 147 | 99.3 | 96.3 | 100 | 362.8 | 307.0 | 428.8 |

Seroprotection = Anti-Poliovirus 1, 2, and 3 antibodies ≥ 8 $ED_{50}$
GMT = geometric mean titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with antibody titres above the cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE= Blood sample taken prior to dose 1
VIS05 M 4= Blood sample taken 1 month after dose 3 of DTPa

**Figure 15** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 (Total vaccinated cohort – Immunogenicity sub cohort 1)**

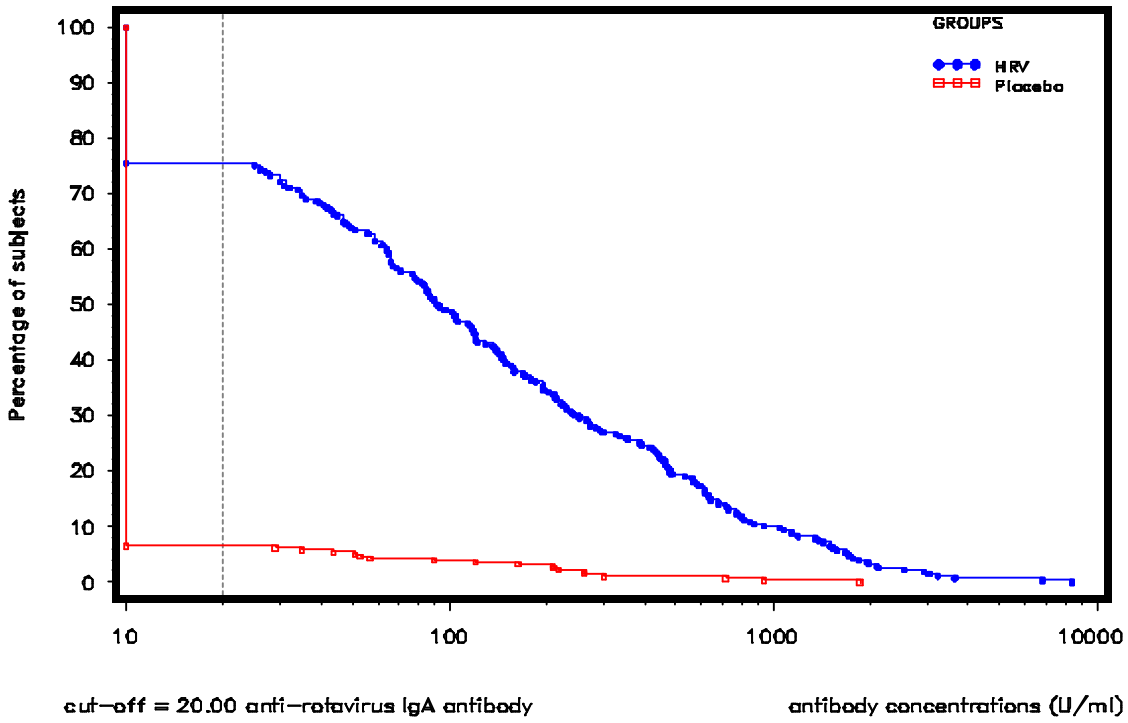


**Figure 16** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 (Total vaccinated cohort – Immunogenicity sub cohort 2)**

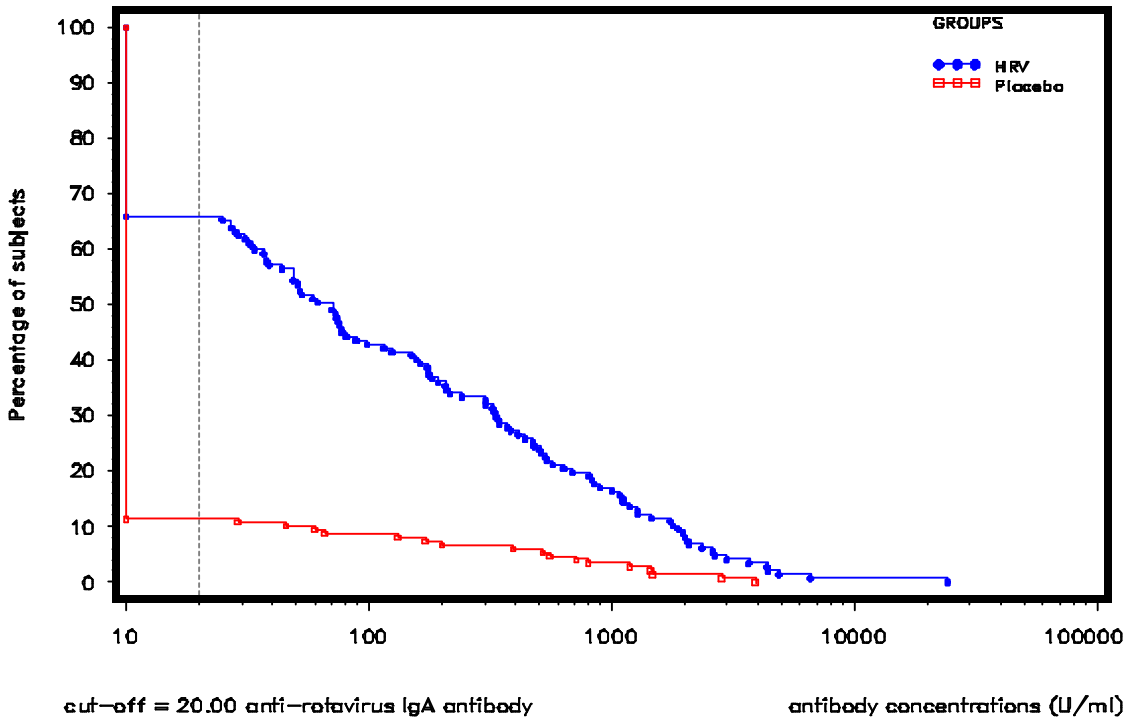


**Figure 17** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 3 (Total vaccinated cohort - Immunogenicity cohort)**

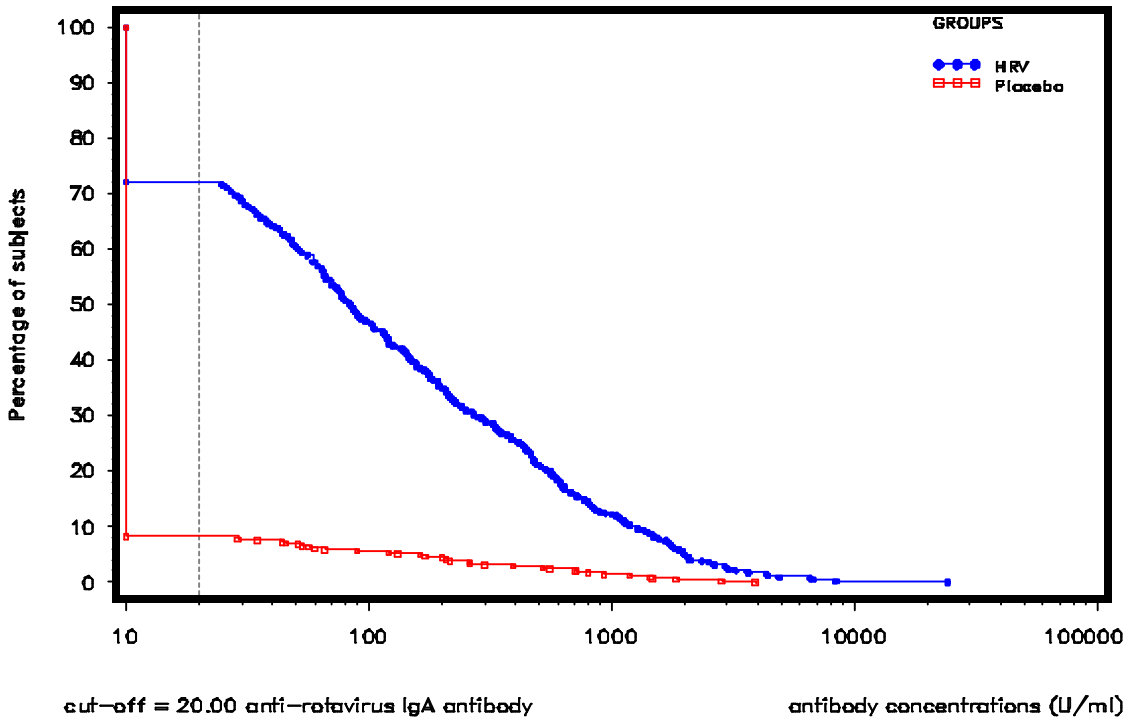


**Figure 18** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 6 (Total vaccinated cohort – Immunogenicity sub cohort 1)**

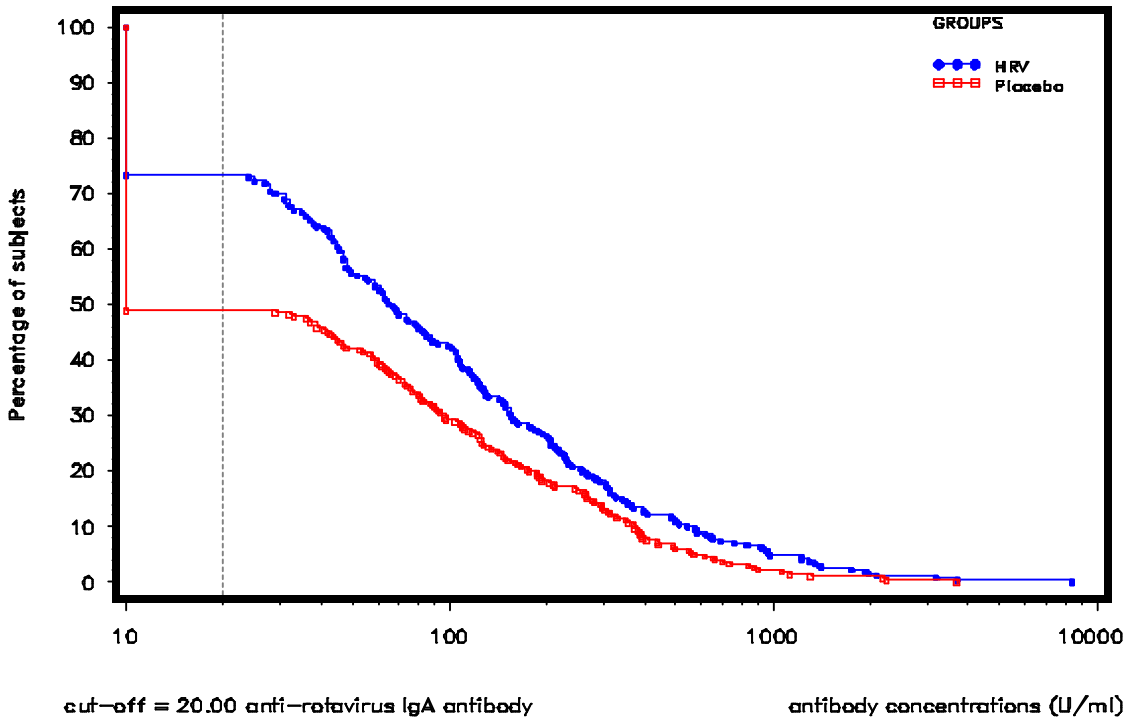


**Figure 19** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 6 (Total vaccinated cohort – Immunogenicity sub cohort 2)**

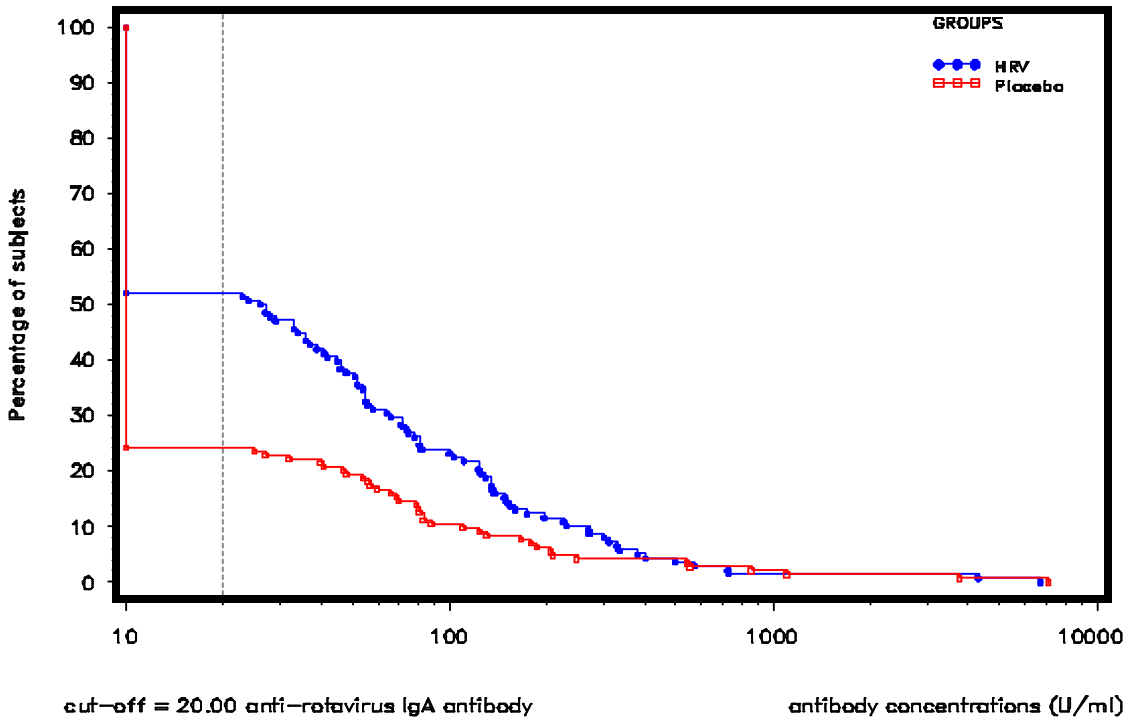


**Figure 20** **Reverse cumulative curves for anti-rotavirus IgA antibody concentrations at Visit 6 (Total vaccinated cohort - Immunogenicity cohort)**

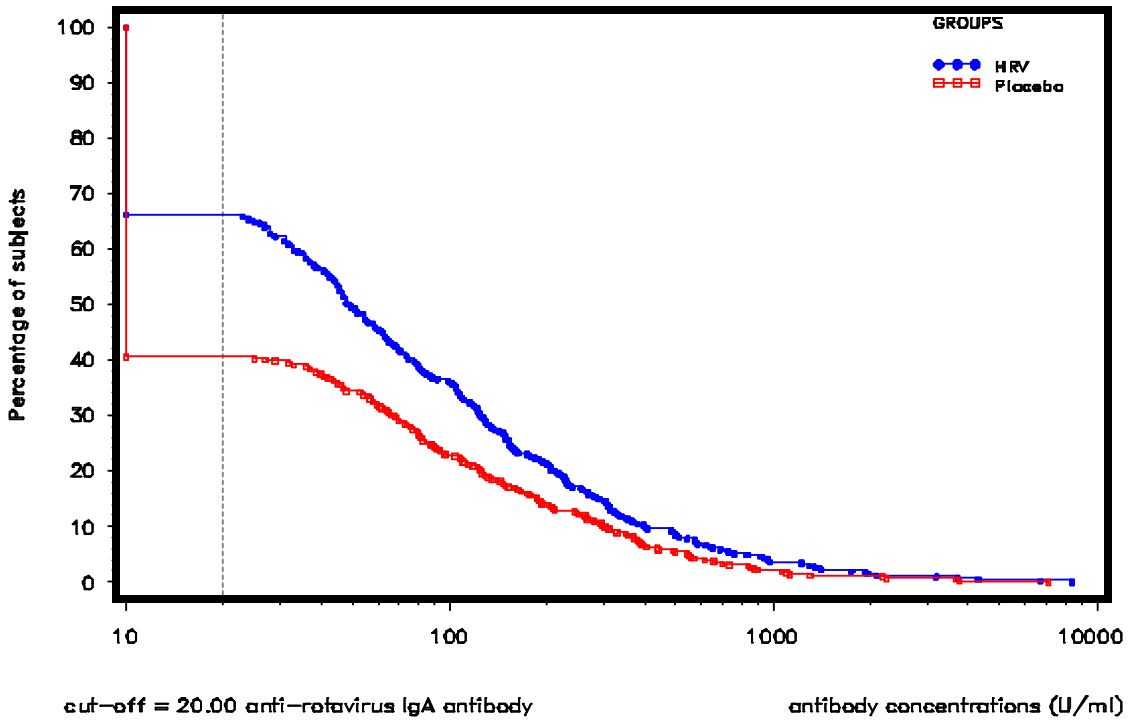


**Figure 21** **Reverse cumulative curves for anti-diphtheria antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

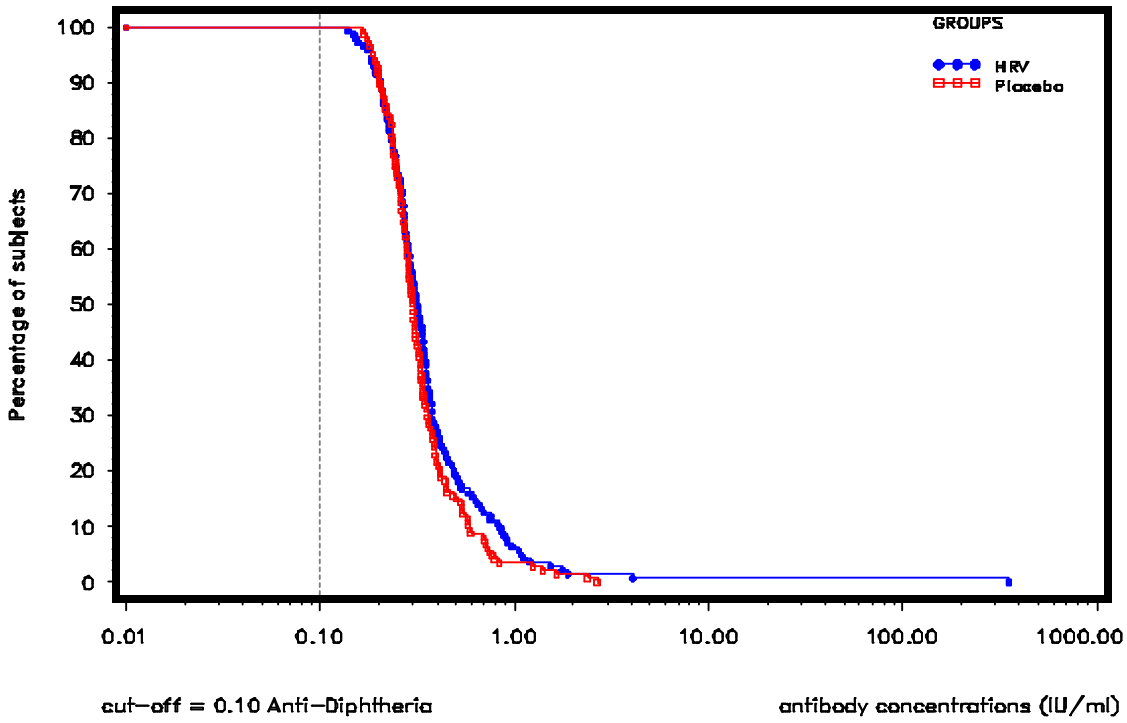


**Figure 22** **Reverse cumulative curves for anti-tetanus antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

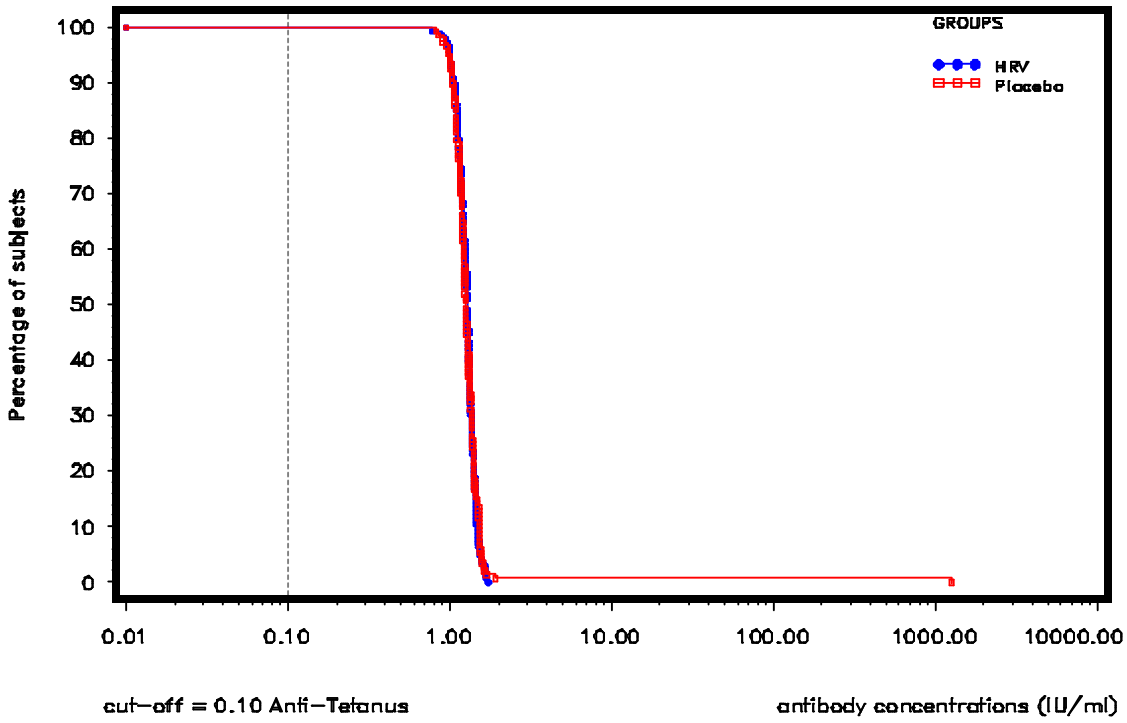


**Figure 23** **Reverse cumulative curves for anti-polio 1 antibody titres at two months post dose 3 of OPV vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

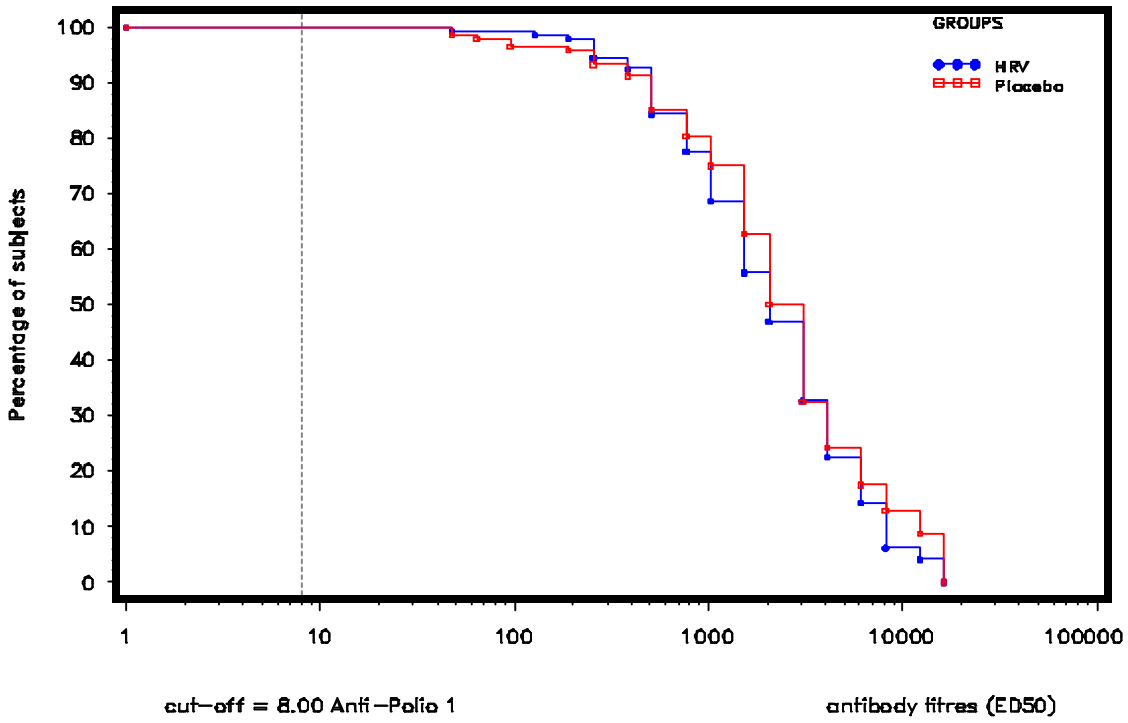


**Figure 24** **Reverse cumulative curves for anti-polio 2 antibody titres at two months post dose 3 of OPV vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

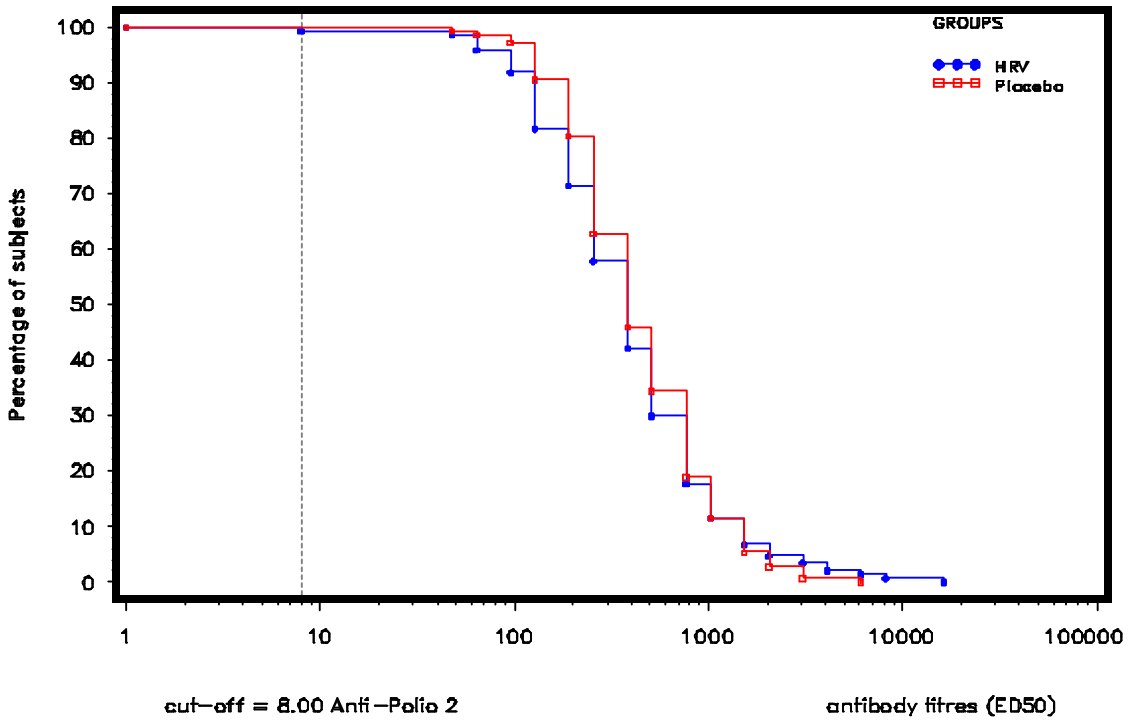


**Figure 25** **Reverse cumulative curves for anti-polio 3 antibody titres at two months post dose 3 of OPV vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

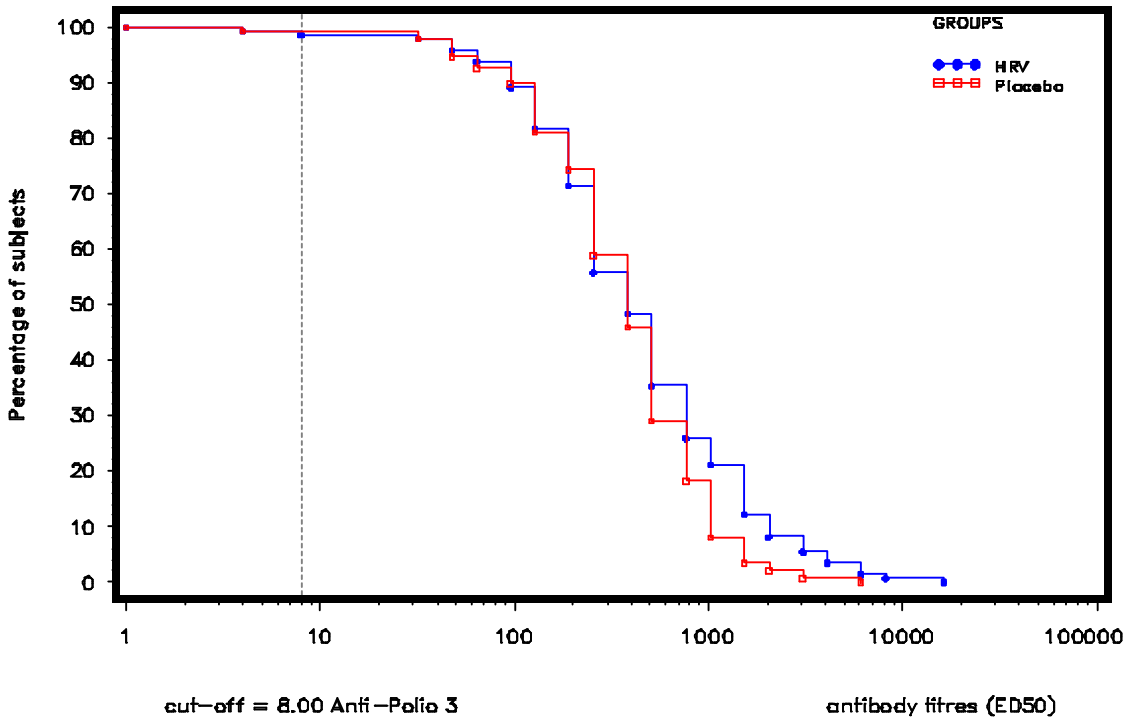


**Figure 26** **Reverse cumulative curves for anti-FHA antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

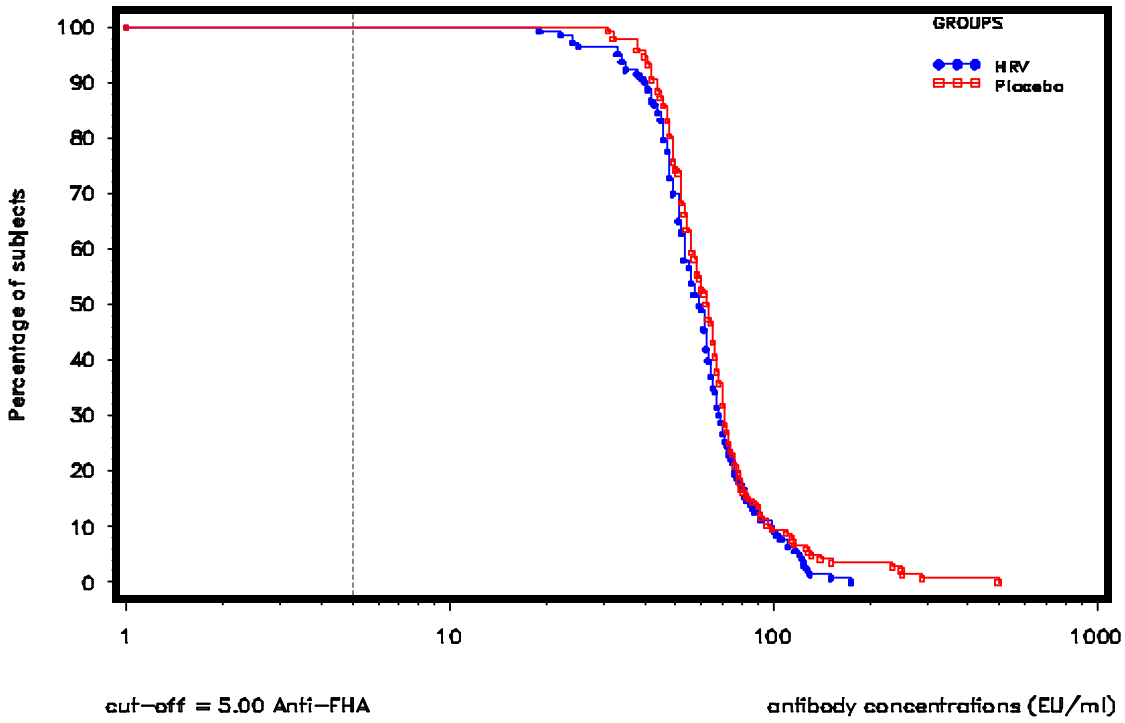


**Figure 27** **Reverse cumulative curves for anti-PT antibody concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**

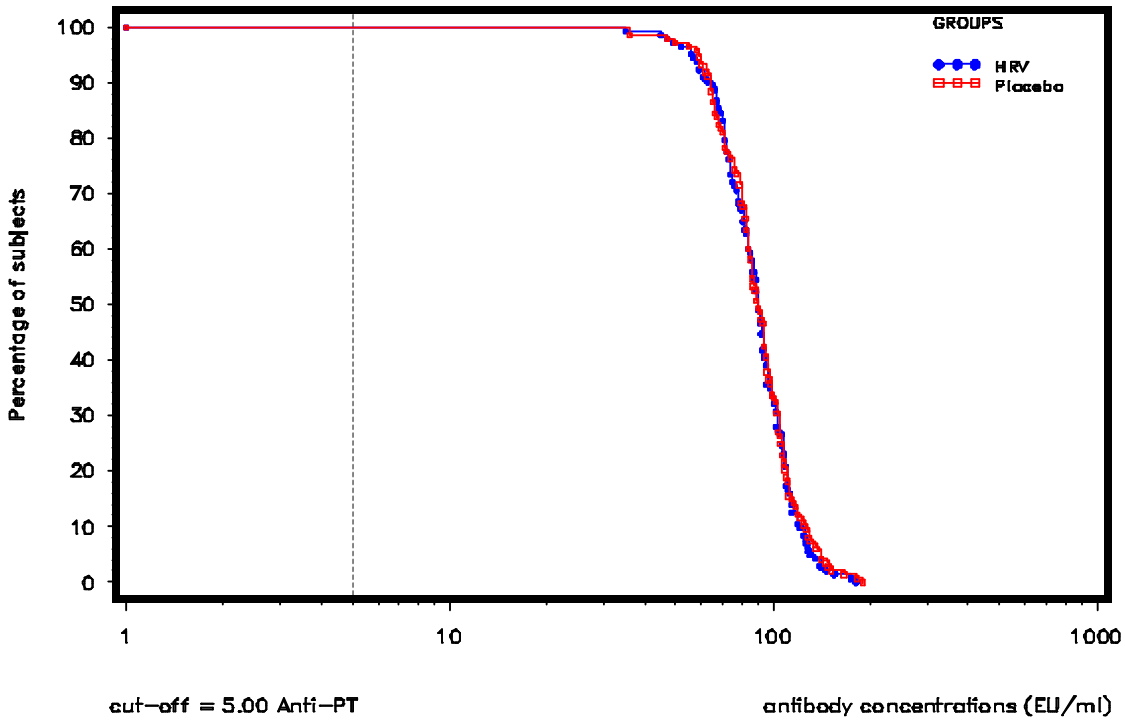
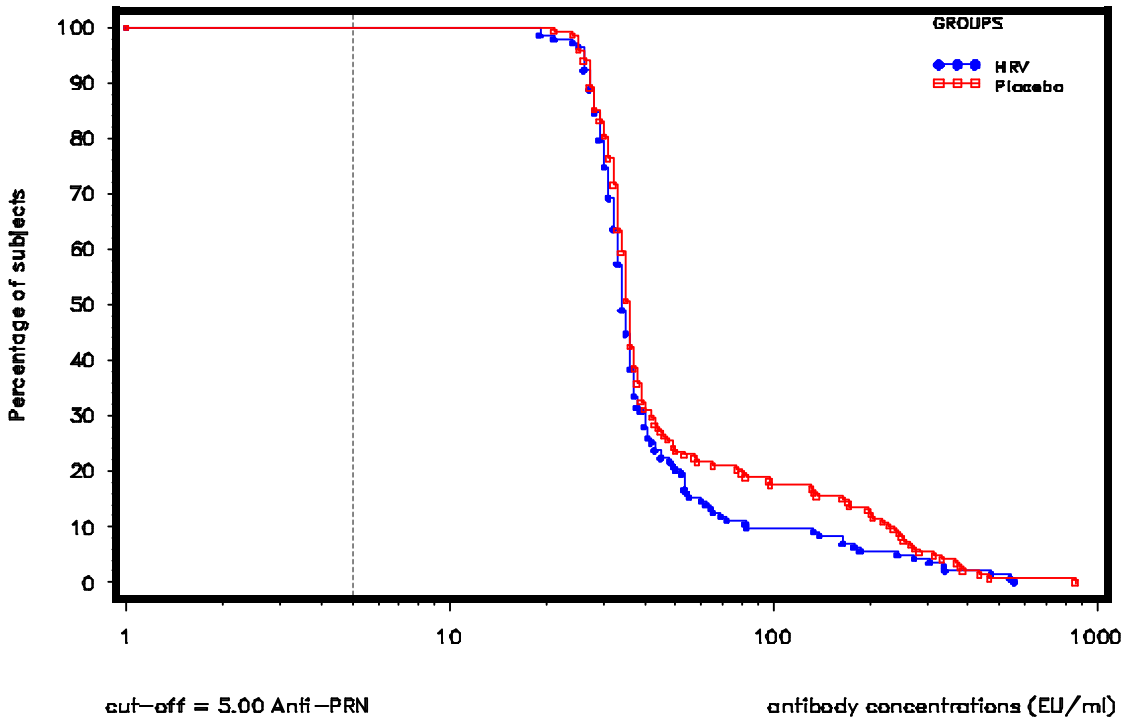


**Figure 28** **Reverse cumulative curves for anti PRN concentrations at one month post dose 3 of DTPa vaccine (Total vaccinated cohort - Immunogenicity sub cohort 2)**



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# 11. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Global Study Manager: [redacted]

Central Safety Contact: [redacted]

Clinical Development Manager: [redacted]

Regulatory Affairs representative: [redacted]

N + 1 of CDM: [redacted]

# 12. SERIOUS ADVERSE EVENTS / OTHER SIGNIFICANT ADVERSE EVENTS / PREGNANCY

Not applicable.

# MODULAR APPENDICES

**List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering. For the majority of the following appendices, see 113808 (ROTA-075) clinical study report, unless otherwise specified.**

| 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 (updated) | 16.1.5 |
| Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used (if applicable). | 16.1.6 |
| Randomization list (patient identification and treatment assigned). | 16.1.7 |
| Audit certificates (if available). | 16.1.8 |
| Documentation of statistical methods | 16.1.9 |
| Documentation of inter-laboratory standardization methods and quality assurance procedures, if used | 16.1.10 |
| Publications based on the study. | 16.1.11 |
| Important publications referenced in the report (updated) | 16.1.12 |
| Individual listings (updated) | 16.2 |
| Case report forms (CRFs /eCRFs)<br>CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events | 16.3<br>16.3.1 |

## Signature of principal or coordinating investigator

**GlaxoSmithKline Biologicals**
**Vaccine Value and Health Science**
**Investigator Approval Page**

Please note that by signing this page, you take responsibility for the content of the Annex Study Report, including appendices

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

Study: 113808 (ROTA-075) 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: | Dr. [redacted] |
| Affiliation /investigational centre: | [redacted] |
| Signature of Investigator: | _____ |
| Date: | _____ |

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# Vaccine Value and Health Science
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STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

Study: 113808 (ROTA-075) Development Phase: III

*I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Clinical Development, DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development

GlaxoSmithKline Biologicals.

Signature: _____

Date: _____

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*This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.*

# GlaxoSmithKline Biologicals
# Vaccine Value and Health Science
# Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Annex Study Report, including appendices

STUDY TITLE: A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

Study: 113808 (ROTA-075) Development Phase: III

*I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Clinical Development, DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development

GlaxoSmithKline Biologicals.

Signature: [redacted]

Date: Aug 28, [redacted] 2013

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*This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.*

## GlaxoSmithKline Biologicals

### Study title

Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants.

### Study detailed title

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

# Clinical Study Report for Study 113808 (ROTA-075)

**Development Phase III**

**IND Number: 2009L10238**

**Indication Studied:** Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

| | |
|---|---|
| **Study initiation date:** | 29 August 2010 |
| **Study completion date:** | 12 May 2012 |
| **Data lock point (Date of database freeze):** | 31 August 2012 |
| **Date of report amendment 1:** | Final 14 August 2013 |
| **Earlier Study Reports** | Report 29 October 2012<br>Annex Report 08 August 2013 |
| **Report Scope:** | This clinical study report presents the final analysis of efficacy, safety and reactogenicity observed during the entire study period. |

**Sponsor Signatory:** [redacted]
Director, Lead Clinical Development,
DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development
GlaxoSmithKline Biologicals.

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

*GSK Biologicals' Study Report INS-BIO-CLIN-1010 v03*

# Foreword

**Study title**

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid HRV vaccine in healthy Chinese infants.

**Name of the Investigational Product:** GSK Biologicals' oral live attenuated HRV vaccine (Rotarix™).

**Name of the Sponsor:** GSK Biologicals, Rixensart, Belgium.

| | |
|---|---|
| **Study Start Date** | 29 August 2010 |
| **Study End date** | 12 May 2012 |

**Name of the Principal Investigator:** Dr. [redacted]

**Address of the Study centre:** [redacted] China.

**Date of the study report**: 29 October 2012

**Date of the amended study report:** 14 August 2013

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| **Name of the Sponsor contacts at GSK:** | [redacted] Director, Lead Clinical Development, DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development GlaxoSmithKline Biologicals. |

**Storage of source documents pertaining to the study:**

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| **At the Investigator site:** | [redacted] China |
| **At GSK China:** | 19, Shunchi Road, Beijing Airport Logistics Zone, Shunyi Distric, Beijing, 101300, China. |
| **At GlaxoSmithKline Biologicals:** | Not applicable |

**Summary of the Report: Please refer to the** SYNOPSIS (REPORT SUMMARY)**.**

# SYNOPSIS (REPORT SUMMARY)

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

**Study No.:** 113808 (ROTA-075)

**Title of the study:** A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

**Principal investigator**: This study was conducted at four centres and Dr. [redacted] was the Principal Investigator for the study.

**Study Centres:** This study was conducted at 4 centres in China.

**Publication (reference):** Not published as of : ***14 August 2013***

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| **Study period:**<br>**Study initiation date:** 29 August 2010<br>**Study completion date:** 12 May 2012<br>**Data lock point (Date of database freeze):** 31 August 2012 | **Phase:** III |

**Indication:** Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

**Treatment:**

The study groups were as follows:

- Group HRV vaccine (Planned, N = 1625)
- Group Placebo (Planned, N = 1625)

Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.

There were two sub-cohorts in this study as described below.

- Immunogenicity Sub-cohort 1 (N=600)
- Immunogenicity Sub-cohort 2 (N=300).

Subjects in each group received routine childhood vaccinations according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 received DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose.

**Objectives:** The study objectives considered for analyses presented in this study report are listed below. Immunogenicity objectives will be presented in a separate annex report.

**Primary**

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective was reached when the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy was at least 10%.

**Secondary**

***Efficacy:***

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation

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due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

**Reactogenicity and Safety:**

***All subjects except subjects in the immunogenicity sub-cohort 2:***

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

***Subjects in the immunogenicity sub-cohort 2:***

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

***All subjects:***

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

**Study design:**

This was a double-blind, randomised, placebo controlled, multi-centric and single-country study with two parallel groups (Group HRV vaccine and Group Placebo). Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1. The study comprised of 7 visits [Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2), Visit 4 (Month 3), Visit 5 (Month 4), Visit 6 (at approximately 1 year of age) and Visit 7 (at approximately 20 months of age) at end of the rotavirus season in China (approximately April 2012)]. Blood samples were to be collected from the sub-cohorts as follows:

- **Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600):**
  - Three blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1, at Visit 3 and at Visit 6.
- **Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300)**:
  - Four blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1, at Visit 3, at Visit 5 and at Visit 6.

Active follow-up for the occurrence of GE* episodes was conducted during the study period via telephone contact or by other means (at least every 2 weeks).

*Note: GE was defined as diarrhoea with or without vomiting. As per the protocol, the final analysis was to be done once 40 severe RV GE episodes caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or at study conclusion, whichever was the earliest. Based on the preliminary review of GE episodes reported prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate during the first RV season seemed lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up was extended till approximately April 2012 (i.e. end of RV season in China).

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

*Vaccination schedule /site*: Subjects were to receive two oral doses of liquid HRV vaccine according to a 0, 1 month schedule.

*Vaccine composition /dose /lot number:* Each 1.5 ml dose of GSK Biologicals' liquid HRV vaccine contained at least $10^{6.0}$ median Cell Culture Infective Dose ($CCID_{50}$*) of RIX4414 HRV strain, ***2.26 mg of*** Dulbecco's Modified Eagle Medium, ***132.74 mg of*** Di-sodium Adipate and ***55% of*** sucrose (w/w). Lot number AROLA219B, [Expiry date: 30 September, 2012] was used for the liquid HRV vaccination.
**(Amended 14 August 2013)**

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**Reference vaccine /Comparator, dose and mode of administration, lot no.:**
*Vaccination schedule /site:* Subjects were to receive two oral doses of the placebo according to a 0, 1 month schedule.
*Vaccine composition /dose /lot number:* Each 1.5 ml dose of GSK Biologicals' placebo contained 2.26 mg of DMEM, 132.74 mg of Di-sodium Adipate and 55% of sucrose (w/w). Lot number PROLA008A, [Expiry date: (31 October 2012)] was used for the placebo. **(Amended 14 August 2013)**

**Routine vaccines, dose and mode of administration, lot no.:**
*Vaccination schedule /site:* Subjects were to receive three doses of Diphtheria-tetanus- acellular pertussis (DTPa) vaccine as intramuscular injections.
*Vaccine composition /dose /lot number:* Each 0.5 ml dose of GSK Biologicals' DTPa vaccine (Infanrix™) contained Diphtheria toxoid ≥ 30 international units (IU), 25 Limits of flocculation (Lf), Tetanus toxoid ≥ 40 IU, (10Lf) Pertussis toxoid 25 µg, Filamentous haemagglutinin 25 µg, Pertactin 8 µg and Aluminium as salts 0.5 mg 2-phenoxyethanol ≤ 2.5 mg. Lot number (YC14B113AA), [Expiry date: 01 July, 2012] was used for the DTPa vaccination.
*Vaccination schedule /site:* Subjects were to receive three oral doses of Oral poliovirus vaccine (OPV) vaccine.
*Vaccine composition /dose /lot number:* Each dose of 0.1 ml (2 drops) of Institute of Medical Biology Chinese Academy of Medical Sciences' OPV contained Total polio-virus not less than 6.15lg $CCID_{50}$ type1, not less than 6.0 $lgCCID_{50}$, type2, not less than 5.0 $lgCCID_{50}$, type3, not less than 5.5 $lgCCID_{50}$. Lot number [20100202], [Expiry date: 01 February, 2012] was used for the OPV vaccination.

**Study Population (Selection of subjects):**
The study population included healthy male/ female infants of Chinese origin aged between 6 and 16 weeks (42-112 days) at the time of the first vaccination who were born after a gestation period of 36 to 42 weeks inclusive. Written informed consent was obtained from the parents/legally acceptable representatives (LARs) of these subjects.

**Duration of study:**
The subjects were followed for approximately 21 months i.e. from study start up to the study end.

The study endpoints considered for analyses presented in this study report are listed below. Immunogenicity endpoints will be presented in a separate annex report.

**Primary Outcome/Efficacy Variable:**

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

**Secondary Outcome/Efficacy Variables:**

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

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- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

*Reactogenicity and Safety:*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs:
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

**Statistical methods:**

***Demography:***

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 were calculated per group and overall. The racial and gender composition was presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall.

***Analysis of Efficacy***

The according-to-protocol (ATP) cohort for efficacy was used for the primary analysis of efficacy. An analysis of efficacy based on the total vaccinated cohort (TVC) was also performed.

During the efficacy follow-up period (2 weeks post Dose 2 to Visit 7 for the ATP cohort), vaccine efficacy was calculated, with their 95% CI against:

- severe RV GE caused by the circulating wild-type RV strains.
- any RV GE caused by the circulating wild-type RV strains.
- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains.
- any and severe RV GE due to each non-G1 type.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains.
- any and severe all cause GE.

Vaccine efficacy was also derived from a Cox regression model on the time to first event with censoring

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for subjects without an event as an additional supportive and exploratory analysis.
Vaccine efficacy analysis was also performed on the data collected from 2 weeks post Dose 2 of HRV vaccine /placebo up to Visit 6. This was presented as an additional supportive analysis.
The same analysis was also performed on Total Vaccinated Cohort from Dose 1 to Visit 6 and Dose 1 to Visit 7 (study end).

***Analysis of Safety (solicited AEs):***

The analysis of safety was based on the TVC. As the percentage of enrolled subjects excluded from the ATP cohort for safety was lower than 5% in both groups, analysis based on the ATP cohort was not performed.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) reported during the solicited follow-up period was tabulated by group, for each dose, for overall doses and per subject. The same calculations were performed for any grade 3 symptoms (solicited or unsolicited) and for any symptom (solicited or unsolicited) related to vaccination.
The incidence, with exact 95% CI, of each individual solicited general symptom, was calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations were done for each individual solicited general symptoms graded as intensity 3 and for each individual solicited general symptom casually related to vaccination. Note: Intensity of fever was assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale was performed separately.
The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term.

- Occurrence of fever was reported per 0.5°C cumulative temperature increments.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects for whom at least one local AE (solicited and unsolicited) was reported after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination were tabulated with exact 95% CI. The same calculations were performed for any grade 3 (solicited or unsolicited) symptoms, grade 3 related symptoms and for any symptoms that required medical attention.
- The percentage of subjects for whom each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa was reported during the 8-day (Days 0–7) follow-up period with exact 95% CI were tabulated.

***Analysis of Safety (unsolicited AEs and SAEs):***

**For all subjects:**

SAEs reported during the study period (i.e. from first vaccine dose to study end) were described in detail. There was a retrospective follow-up on SAEs for subjects who had already completed Visit 6 prior to the implementation of protocol amendment 2.
The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.
The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

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**Study population (Total vaccinated cohort)**

| **Number of subjects** | **HRV group** | **Placebo group** |
|---|---|---|
| Planned, N | 1625 | 1625 |
| Randomised, N (Total Vaccinated Cohort) | 1666 | 1667 |
| Completed, n (%) | 1518 (91.1) | 1499 (89.9) |
| **Demographics** | **HRV group** | **Placebo group** |
| N (Total Vaccinated Cohort) | 1666 | 1667 |
| Females: Males | 795:871 | 836:831 |
| Mean Age, weeks (SD) | 9.5 (2.64) | 9.7 (2.59) |
| Asian-Chinese heritage, n (%) | 1666 (100) | 1667 (100) |

SD=Standard deviation
Completed= number of subjects who completed last study visit

**Summary (Study results):**

Immunogenicity results will be presented in a separate annex report.

***Efficacy Results:***

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV was 72.0% [95% CI: 54.1%; 83.6%]. Severe RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (1.3% versus 4.8%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7. The primary objective of the study was met since the lower limit of the 95% CI on vaccine efficacy was above 10% (pre-specified criteria for the primary efficacy objective).
- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.1% [95% CI: 44.3%; 68.8%]. RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (4.4% versus 10.6%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating wild type G1 was 52.2% [95% CI: 19.0%; 72.6%] and 64.0% [95% CI: 20.4%; 85.2%], respectively. Vaccine efficacy against severe RV GE caused by circulating wild type G1P[8] was 60.1% [95% CI: 5.3%; 84.8%]. Vaccine efficacy against any RV GE caused by G1P[8] was 47.4% [95% CI: 7.4%; 71%, p-value 0.024].Fewer subjects in the HRV group reported any and severe RV GE caused by circulating wild-type G1 compared to the placebo group (1.4% and 0.6% versus 2.9% and 1.6% , respectively, p-value 0.005 and 0.009) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating non-G1 type was 62.1% [95% CI: 46.9%; 73.3%] and 77.8% [95% CI: 58.0%; 89.2%], respectively. Fewer subjects in the HRV group reported any and severe non-G1 type RV GE episode compared to the placebo group (3.1% and 0.8% versus 8.2% and 3.4%, respectively, p-value <0.001 for both) from 2 weeks post-Dose 2 up to Visit 7. Vaccine efficacy against any RV GE caused by G2P[4] was 58.9% [95% CI: 40.5%; 72.0%, p-value <0.001].Vaccine efficacy against severe RV GE caused by G2P[4] was 72.5% [95% CI: 45.5%; 87.3%].
- Vaccine efficacy against RV GE caused by circulating wild-type RV that required hospitalization was 81.0% [95% CI: 43.6%; 95.3%]. Fewer subjects in the HRV group required hospitalization following an episode of RV GE as compared to the placebo group (0.3% versus 1.3%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against RV GE leading to hospitalization or requiring rehydration therapy was 66.4% [95% CI: 49.6%; 78.1%]. Fewer subjects in the HRV group were hospitalized and/or

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required rehydration therapy following an episode of RV GE as compared to the placebo group (2.1% versus 6.2%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.

- Vaccine efficacy against all cause GE was 4.2% [95% CI: -6.2%; 13.6%]. All cause GE episodes reported for subjects in HRV group and placebo group was similar (46.2% versus 48.3%, p-value 0.422) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause severe GE was 9.3% [95% CI: -11.1%; 26.0%]. All cause severe GE episodes for subjects in HRV group and placebo group was similar (11.92% versus 13.1%, p-value: 0.357) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause GE that required hospitalization was 41.2% [95% CI: 13.1%; 60.6%]. Fewer subjects in the HRV group required hospitalization following an episode of all cause GE as compared to the placebo group (2.7% versus 4.6%, p-value 0.007) from 2 weeks post Dose 2 up to the Visit 7.

Percentage of subjects for whom severe (Vesikari score greater than or equal to 11) RVGE episode was reported and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | | | n/N | | | VE | | | |
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| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 21 | 1.3 | 0.8 | 2.0 | 72.0 | 54.1 | 83.6 | <0.001 |
| Placebo | 1573 | 75 | 4.8 | 3.8 | 5.9 | - | - | - | - |

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

***Reactogenicity and Safety Results:*** The analysis of safety was performed on the Total vaccinated cohort.
***Any Symptom:***
**All subjects except immunogenicity sub-cohort 2:**

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any AEs (solicited or unsolicited) was 44.2% [95% CI: 41.7%; 46.8%] subjects in the HRV group and 47.3% [95% CI: 44.8%; 49.8%] subjects in the placebo group. Any AEs (solicited or unsolicited) were reported for 32.8% [95% CI: 30.4%; 35.2%] and 26.6% [95% CI: 24.4%; 29.0%] subjects after the first and second dose of HRV vaccine respectively. Any AEs (solicited or unsolicited) assessed as causally related to vaccination were reported by 15.8% [95% CI: 14.0%; 17.7%] subjects in HRV group and 14.7% [95% CI: 12.9%; 16.5%] subjects in the placebo group. No more than 11.2% of the subjects in both groups reported any AEs (solicited or unsolicited) rated as grade "3" in intensity.

**All subjects in the immunogenicity sub-cohort 2:**

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any general symptoms (solicited or unsolicited) was 52.9% [95% CI 44.7%; 61.1%] subjects in the HRV group and 50.3% [95% CI: 42.1%; 58.5%] subjects in the placebo group. Any general symptoms (solicited or unsolicited) were reported for 42.5% [95% CI: 34.5%; 50.7%] and 30.0% [95% CI: 22.8%; 38.0%] subjects after the first and second dose of HRV vaccine, respectively. No more than 16.0% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.

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- During the 8-day follow-up period (Day 0 to Day 7), any general symptoms (solicited or unsolicited) rated as grade "3" in intensity and causally related to vaccination were reported for 2.6% [95% CI: 0.7%; 6.6%] subjects in the HRV group and 2.0% [95% CI: 0.4%; 5.6%] subjects in the placebo group. No more than 1.3% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.
- During the 8-day follow-up period (Day 0 to Day 7), any AEs (solicited or unsolicited) requiring medical attention were reported for 12.4% [95% CI: 7.6%; 18.7%] subjects in the HRV group and 11.1% [95% CI: 6.6%; 17.2%] subjects in the placebo group.

***Solicited symptoms:***

**All subjects except immunogenicity sub-cohort 2:**

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 27.4% subjects in the HRV group and 29.6% subjects in the placebo group. Irritability/fussiness was reported for 21.5% [95% CI: 19.4%; 23.6%] and 12.9% [95% CI: 11.2%; 14.7%] subjects after the first and second dose of HRV vaccine, respectively.

**All subjects in the immunogenicity sub-cohort 2:**

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 36.6% subjects in the HRV group and 34.0% subjects in the placebo group. Irritability/fussiness was reported for 28.8% [95% CI: 21.7%; 36.6%] and 18.7% [95% CI: 12.8%; 25.8%] subjects after the first and second dose of HRV vaccine, respectively. No more than 3.3% of the subjects in both groups reported irritability/fussiness rated as grade "3" in intensity.
- During the 8-day (Day 0- Day 7) follow-up period, redness was the most frequently reported solicited local symptom for 13.3% subjects in the HRV group and 8.6% subjects in the placebo group. The most frequently reported grade "3" solicited local AEs were pain for 1.3% of subjects in the HRV group and redness for 0.7% of subjects in the placebo group. The solicited local symptoms were related to DTPa vaccine given intramuscularly.

**All subjects:**

***Unsolicited symptoms:***

- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 18.6% in the HRV group and 22.1% in the placebo group.
- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one grade "3" unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 0.1% in the HRV group and 0.2% in the placebo group. The percentage of subjects reported for unsolicited AEs assessed as causally related to vaccination was 0.5% in the HRV group and 0.4% in the placebo group.

***Serious adverse events:***

- During the study period, the percentage of subjects reported for at least one SAE was 11.0% (183/1666) in the HRV group and 14.8% (246/1667) in the placebo group. [redacted] None of the SAEs reported in the HRV group were causally related to the vaccine as assessed by the investigator. [redacted]
- Of the 13 deaths (6 in the HRV group and 7 in the placebo group) reported during the study period,

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

none of the fatal SAEs were assessed as causally related to vaccination by the investigator.

***Withdrawals due to adverse events /serious adverse events:***

- Eighteen subjects (8 in the HRV group and 10 in the placebo group) experienced unsolicited AEs or SAEs, leading to premature discontinuation from the study.

**Conclusion:**

Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV during the efficacy follow up period (2 weeks post-Dose 2 up to Visit 7) was 72.0% [95% CI: 54.1%; 83.6%]. The primary objective of this study was met.

**Date of report amendment 1:** Final: 14 August 2013

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ATP** | According-To-Protocol |
| **$CCID_{50}$** | Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells) |
| **CI** | Confidence Interval |
| **DMEM** | Dulbecco's Modified Eagle Medium |
| **DTPa** | Combined Diphtheria, Tetanus and acellular Pertussis vaccine |
| **eCRF** | electronic Case Report Form |
| **$ED_{50}$** | Estimated dose 50% |
| **EL.U/mL** | ELISA Units per Millilitre |
| **ELISA** | Enzyme Linked Immunosorbent Assay |
| **EPI** | Expanded Program on Immunisation |
| **FHA** | Filamentous Haemagglutinin |
| **GCP** | Good Clinical Practice |
| **GE** | Gastroenteritis |
| **GMC** | Geometric Mean Concentration |
| **GSK** | GlaxoSmithKline |
| **GSM** | Global Study Manager |
| **HRV** | Human Rotavirus |
| **IB** | Investigator Brochure |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IgA** | Immunoglobulin A |
| **IM** | Intramuscular |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **IS** | Intussusception |
| **IU/mL** | International Units per Millilitre |
| **LAR** | Legally Acceptable Representative |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **Mg** | Milligram |

| | |
|---|---|
| **mL** | Millilitre |
| **MMWR** | Morbidity and Mortality Weekly Report |
| **NIFDC** | National Institute for Food and Drug Control |
| **O** | Oral |
| **OPV** | Oral Poliovirus vaccine |
| **PCR** | Polymerase Chain Reaction |
| **PRN** | Pertactin |
| **PT** | Pertussis toxoid |
| **RV** | Rotavirus |
| **SAE** | Serious Adverse Event |
| **SAS** | Statistical Analysis System |
| **SBIR** | Internet Randomisation tool |
| **SDV** | Source Document Verification |
| **SFDA** | State Food and Drug Administration |
| **SPM** | Study Procedures Manual |
| **U/mL** | Units per Millilitre |
| **UA** | Upper Arm |
| **UMV** | Universal Mass Vaccination |
| **VE** | Vaccine Efficacy |
| **WHO** | World Health Organisation |

## GLOSSARY OF TERMS

| | |
|---|---|
| **According-To-Protocol cohort:** | This cohort included all subjects enrolled in the study who meet the criteria defined in the protocol for the considered analysis (Efficacy, reactogenicity and safety). |
| **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.<br><br>An AE was therefore 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 included failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. |
| **Blinding:** | A procedure in which one or more parties to the trial were kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. 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. The level of blinding was maintained throughout the conduct of the trial, and only when the data were cleaned to an acceptable level of quality appropriate personnel unblinded or when required in case of a serious adverse event (SAE). |
| **Child in care:** | A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted nor has an appointed legal guardian. |
| **Completed:** | Subjects who were available for the study concluding visit. |
| **Diarrhoea:** | Passage of three or more looser than normal stools within a day. |

| | |
|---|---|
| **Diary card:** | Cards given to the parents /guardians by the investigator to record adverse events following vaccination. |
| **Eligible:** | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |
| **Epoch:** | An epoch was a self-contained set of consecutive time-points or a single time-point from a single protocol. Self-contained meant that data collected for all subjects at all time-points within that epoch allowed to draw a complete conclusion to define or precise the targeted label of the product. Typical examples of epochs are primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety. |
| **eTrack:** | GSK's tracking tool for clinical trials. |
| **Evaluable:** | Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis. |
| **Gastroenteritis:** | Diarrhoea with or without vomiting. |
| **Investigational vaccine/product:**<br><br>**(Synonym of Investigational Medicinal 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. |
| **Legally Acceptable Representative:** | ICH GCP defines Legally Accepted Representative (LAR) as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. |
| **Protocol amendment:** | The International Conference on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study. |
| **Randomisation:** | Process of random attribution of treatment to subjects in order to reduce bias of selection. |

| | |
|---|---|
| **Serious adverse event:** | 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 event 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. |
| **Severe rotavirus gastroenteritis:** | An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system). |
| **Solicited adverse events:** | AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events was actively solicited from the subject's parent/LAR or an observer during a specified post-vaccination follow-up period. |
| **Sub-cohort:** | A group of subjects for whom specific data are collected compared to other subjects. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Subject:** | Term used throughout the clinical study report to denote an individual who has been contacted in order to participate in the clinical study, either as a recipient of the vaccine(s)/product(s) or as a control. |
| **Symptom sheet:** | Specific pages in the individual case report form onto which the investigator transcribed from the diary card and/or other source documentation on solicited adverse event(s) reported by the parents /guardians (one sheet for solicited local adverse events, one sheet for solicited general adverse events). |
| **Total vaccinated cohort:** | The total vaccinated cohort will include all subjects with at least one vaccine administration documented. A safety analysis based on the total vaccinated cohort will include all vaccinated subjects. An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available. |
| **Treatment number:** | A number identifying a treatment to a subject, according to the study randomisation or treatment allocation. |

| | |
|---|---|
| **Treatment:** | Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation. |
| **Unsolicited adverse event:** | Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms were reported as an unsolicited adverse event. |
| **Vomiting:** | One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day. |

## TRADEMARKS

The following trademarks are used in the present report.

Note: In the body of the Study Report (including the synopsis), the names of the vaccines/products and/or medications will be written without the superscript symbol ™ or ® and in *italics*.

| Trademarks of the GlaxoSmithKline group of companies | Generic description |
|---|---|
| Rotarix™ | Human rotavirus vaccine |
| Infanrix™ | Combined diphtheria-tetanus-acellular pertussis (DTPa) vaccine |

| Trademarks not owned by the GlaxoSmithKline group of companies | Generic description |
|---|---|
| OPV (Institute of Medical Biology Chinese Academy of Medical Sciences') | Poliomyelitis (live) Vaccine (Monkey Kidney Cell), Oral |

# 1. ETHICS

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

The study protocol, two amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre IEC.

## 1.2. Ethical conduct of the study

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

## 1.3. Subject information and consent

Written informed consent was obtained from the parent/ legally acceptable representative (LAR) prior to the performance of any study-specific procedures. Electronic case report forms (eCRFs) were provided for each subject's data to be recorded.

# 2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE (STUDY MANAGEMENT)

## 2.1. Administrative structure

This study was conducted at 4 centres in China by Dr. [redacted] as the principal investigator.

**Responsibilities of the Investigator:**

- Compliance with GCP procedures and applicable local regulations in China.
- Permitting monitoring and auditing by GSK or a GSK designated organisation.
- Maintenance of a list of appropriately qualified persons to whom trial-related duties were delegated.

In terms of the Investigator resources *(ICH-GCP 4.2)*:

- Potential for recruiting potential subjects
- Sufficient time to conduct the trial
- Qualified personnel and adequate training of study personnel
- Adequate facilities at the study centre to conduct the trial.

In terms of obtaining approval from the appropriate IRB/IEC *(ICH-GCP 4.4)*:

Before initiating the trial, the Investigator had to write and date the approval for:

- The trial protocol,
- Written informed consent form and consent form updates (if any),
- Subject recruitment procedures (e.g. advertisements),
- Any other information that was to be provided to the subjects,
- Investigator brochure.

In terms of medical care of trial subjects *(ICH-GCP 4.3)*:

- A qualified physician (Investigator or sub investigator) was responsible for all trial-related medical decisions.

In terms of compliance with the protocol *(ICH-GCP 4.5):*

- The Investigator/Institution was to sign the protocol, or an alternative contract, to confirm agreement to comply with the protocol and was not to implement any deviations without:
  - agreement by the Sponsor,
  - prior review and documented approval from the IRB/IEC of an amendment,
  - except, where necessary to eliminate an immediate hazard(s) to trial subjects or,
  - when changes involved only logistical or administrative aspects of the trial.

In terms of accountability of the investigational product *(ICH-GCP 4.6)*:

- Accountability of the investigational product at the trial site was the sole responsibility of the Investigator, for which the Investigator was to maintain adequate documentation that:
  - doses were provided to subjects as specified in the protocol,
  - reconciliation of all investigational products received from the Sponsor,
  - the investigational product was to be stored and used as specified in the protocol.

In terms of maintenance of trial-related records and reports *(ICH-GCP 4.9.5)*:

- Records were to be accurate, complete, legible and timely pertinent to the data reported [i.e. subjects' hospital records, eCRFs].
- Data reported on the eCRFs were to be derived from the source document.

- All corrections to an eCRF were to be dated, initialed, explained and were not to obscure the original entry.
  **Note**: eCRFs were used in this study and the Remote Data Entry (RDE) application used a built-in system to track any corrections to data.
- The period of retention of all documents was a minimum of 2 years after the last approval of marketing application of the product.
- The Investigator was to permit direct access to all trial-related records and reports to the Sponsor (auditor, monitor), IRB/IEC and regulatory authorities.

In terms of communication with the IRB/IEC:

During trial period, investigator was to forward to the IRB/IEC:

- investigator brochure updates
- written summaries on the status of the trial annually or more frequently (if it was requested)
- the Investigator was to provide written progress reports to the Sponsor and the IRB/IEC on any changes that significantly affected the trial or increased risk to subjects.

If the Investigator terminated or suspended the trial without prior agreement of the Sponsor, the Investigator was to provide detailed written explanation to the Sponsor, the IRB/IEC and the regulatory authorities (if required).

In case premature termination or suspension of a trial the Investigator was to inform trial subjects and assure appropriate therapy and follow-up.

After completion of the trial, the Investigator was to inform and provide the Sponsor, the IRB/IEC all the required reports, a summary of the study outcome and reports to regulatory authorities (if applicable).

Additionally, the Investigator was also responsible for:

- The review of the consent form and appropriate consent procedure *(ICH-GCP 4.8)*
- Reporting of serious adverse events (SAEs) to Sponsor and the IRB/IEC and notification of investigator brochure updates to IRB/IEC *(ICH-GCP 4.11)*.

**Responsibilities of the Study Sponsor:**

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

In terms of implementing and maintaining Quality Assurance (QA) and Quality Control (QC) systems:

- The Sponsor was to ensure that the trial was conducted, data generated and documentation of data (data were reliable and processed correctly) and reported data was in compliance with the protocol, GCP and regulatory requirements.
- The Sponsor was to secure a written agreement with the Investigator (institution and/or parties involved in the clinical trial) to the trial-related site, source data/documents and reports, primarily for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.
- If the Sponsor transferred any trial-related duties and functions to a Contract Research Organisation (CRO), it was the Sponsor's responsibility to ensure:
  - Quality and integrity of trial data. It was the function of the CRO to implement QA and QC
  - Clear explanation of functions that were "not" transferred to the CRO, including the duties and functions of the Sponsor.
- The Sponsor was to designate qualified medical personnel to answer any trial-related medical queries. The Sponsor was also to appoint qualified personnel (biostatisticians, physicians etc) for:
  - designing protocols and eCRFs, analysing data, and for preparation of clinical trial reports/study reports
  - Supervision of the trial and handling and verification of data.
- The Sponsor was to provide guidance to the Investigator on the clinical trial protocol and protocol amendments, including ICH guidance on the structure of the clinical trial.
- For trial management, the Sponsor was to provide Subject Identification Code and retain all Sponsor-specific essential documents.
- In case of discontinuation (termination/suspension) of the clinical trial, the Sponsor was to provide a written explanation to the Investigator and the IRB/IEC.
- In case of transfer of ownership of the trial, the Sponsor was to report this to the relevant authority.
- The Sponsor was to inform the Investigator/Institution that all trial-related documents were to be retained for a minimum of 2 years after the last approval of marketing application of the investigational product. The Sponsor was also to inform the Investigator/Institution regarding the destruction of any documents.
- In terms of selection of the Investigator/Institution for the trial, the Sponsor was to:
  - Select qualified personnel (with experience and resources to conduct the trial). For multicentre trials, the Sponsor was to select a coordinating committee and/or coordinating investigator(s)
  - provide the protocol and the investigator brochure (that included non-clinical/ clinical data)

  - Obtain the Investigator's/Institution's agreement to conduct the trial according to GCP (after obtaining approval from the IRB/IEC), to comply with procedures, to permit monitoring, auditing and inspection and to retain essential documents.

- All trial-related duties and functions were to be defined and established by the Sponsor.
- In terms of providing compensation to the subjects and Investigators, the Sponsor was to:
  - provide insurance against claims arising from the trial (except for malpractice and/or negligence)
  - address costs of treatment (of subjects) i.e. during trial-related injuries
  - Compensation of trial subjects in compliance with applicable regulatory requirement(s).
- The Sponsor was to inform the Investigator/Institution of all financial aspects related to the trial in an agreement.
- The applications required for the trial were to be submitted/notified by the Sponsor to the appropriate authority(ies) for review, acceptance and/or for permission to start the trial.
- For confirmation of review of relevant documents by the IRB/IEC, the Sponsor was to obtain the name and address of the IRB/IEC, if it operated according to GCP and the applicable laws and regulations in the country. The Sponsor was to ensure that there was documentation for the IRB/IEC approval for the protocol, written informed consent form(s), written information provided to subjects, subject recruiting procedures, and documents related to payments.
- The Sponsor was to obtain from Investigator/ Institution a copy of the modification(s) made and the approval date given by the IRB/IEC.
- The Sponsor was to ensure that the investigational product was manufactured according to Good manufacturing Practices with appropriate coding and labeling of products to maintain blinding and identification.
- The Sponsor was to ensure that the investigational product was sent to the investigational site(s) after obtaining appropriate documentation.
- The Sponsor was to ensure that the Investigator/Institution maintained the investigational product under defined storage conditions.
- The Sponsor was to provide written procedures to the Investigator/Institution for the adequate and safe receipt, handling, storage, and dispensing, retrieval of unused investigational product, and return of unused investigational product to the Sponsor (or alternative disposition).
- The Sponsor was to ensure timely delivery of the investigational product. Maintain records for the shipment, receipt, disposition, return and destruction of the investigational product. The Sponsor was to maintain documentation in case the investigational product was retrieved due to expiry or after trial completion.

- The Sponsor was to ensure investigational product stability over the period of use.
- The Sponsor was to provide specifications to the Investigator/Institution for providing direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. This also included access to written informed consent of subjects, direct access to original medical records, audit, IRB/IEC review, and regulatory inspection.
- The Sponsor was to evaluate safety data from the trial regularly and inform the Investigator/Institution and regulatory authority(ies) in case findings affected the safety of subjects in the trial.
- For adverse drug reporting, the Sponsor was to submit safety reports and periodic reports to the regulatory authority(ies).
- The Sponsor was to evaluate trial conduct and compliance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirements by conduct of audits, as appropriate.
- In case of non-compliance to the protocol, SOPs, GCP and/or applicable regulatory requirements by the Investigator/Institution or members of the Sponsor's staff, the Sponsor was to take prompt action.

The Sponsor was to ensure that clinical trial study reports were prepared and provided to the regulatory authority (ies).

## 2.2. Clinical Study Report revision history

***The following missing information/errors were identified:***

- ***Missing values for the liquid formulation of the HRV vaccine in the Synopsis,***
- ***Errors in sucrose content of the liquid formulation of the HRV vaccine and the placebo in Table 5,***
- ***Errors in some references quoted in the discussion section.***

***This report is being amended to make the necessary corrections.***

# 3. INTRODUCTION

## 3.1. Background

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) among young children aged < 5 years. A recent review estimated that RV is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year where the majority of the deaths occur in the developing countries in Asia and Africa [WHO, 2007].

China has the second largest birth cohort in the world and the second highest number of deaths due to RV infection. In China, RV is the most common cause of diarrhoea and an economic burden for the parents. Approximately 27, 000 RV associated deaths occur each year and 32% - 50% of the hospitalised diarrhoea are associated with an RV infection [Naghipour, 2008; Wang, 2009].

In China, introduction of a RV vaccine would most likely be beneficial for children and a significant proportion of the diarrhoeal disease burden might be prevented in the near future [Liu, 2006].

GlaxoSmithKline (GSK) Biologicals had developed a human rotavirus (HRV) vaccine to meet this health need. GSK Biologicals' lyophilised HRV vaccine has been extensively tested in clinical studies conducted in infants from Europe, North America, Latin America and the Caribbean, Asia and Africa. In addition to the lyophilised formulation, GlaxoSmithKline (GSK) Biologicals had also developed a liquid formulation of the human rotavirus (HRV) vaccine.

Please refer to the current Investigator Brochure for a review of the pre-clinical and clinical studies, and the potential risks and benefits of liquid HRV vaccine.

## 3.2. Rationale on study design, vaccine administration schedule and indication

### 3.2.1. Rationale for the study

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of file for licensure in China.

### 3.2.2. Rationale for the study design

This phase III, double-blind, randomised, placebo-controlled, multi-centre study was conducted to assess the efficacy, immunogenicity and safety of GSK Biologicals' liquid HRV vaccine. GSK Biologicals also intends to submit immunogenicity and reactogenicity data of the co-administered routine vaccines to the Chinese State Food and Drug Administration (sFDA). In order to assess the immunogenicity of HRV vaccine and the co-administered routine vaccines, two immunogenicity sub-cohorts were planned to be enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo was to be

assessed in the first sub-cohort (N = 600). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 was to be assessed in the second sub-cohort (N = 300). Reactogenicity of the liquid HRV vaccine/Placebo was assessed in the whole cohort except for the second immunogenicity sub-cohort.

# 4. STUDY OBJECTIVES (PURPOSE OF THE STUDY)

The study objectives considered for analyses presented in this study report are listed below. Immunogenicity objectives will be presented in a separate annex report.

## 4.1. Primary objective

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy is at least 10%.

## 4.2. Secondary objectives

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

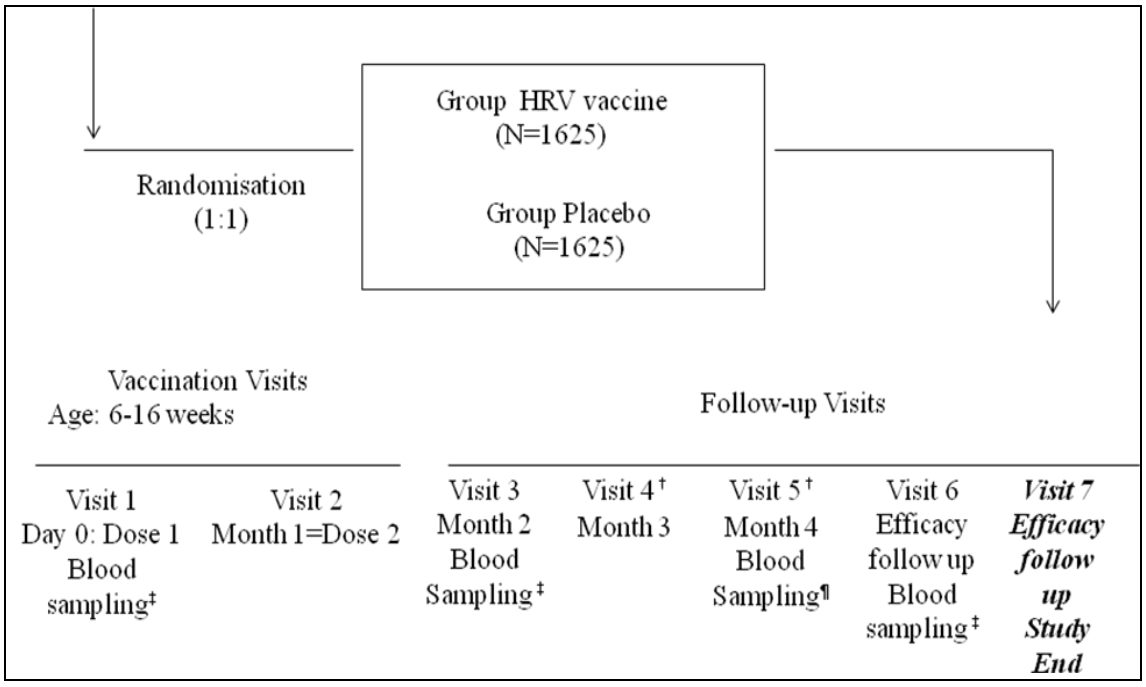
*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

See Section 5.9 for details of the study endpoints.

# 5. INVESTIGATIONAL PLAN

## 5.1. Study design (Overview and description of the protocol)




N: Number of subjects that was planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 was applicable only to subjects in the immunogenicity sub-cohort 2.
‡Blood was drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood was drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 received a dose of OPV at Visit 1, Visit 2 and Visit 3; and received a dose of DTPa at Visit 2, Visit 3 and Visit 4.

### 5.1.1. Overall study design – Description (Discussion of study design)

- Experimental design: Phase III, double-blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: The subjects were to be followed from study start until approximately April 2012 (i.e. end of RV season in China). The duration of the study, per subject, did not exceed a maximum of 21 months. The study had a single epoch as follows.
  - Primary Epoch: Primary epoch started at Visit 1 (Day 0) and ended at Visit 7 (approximately April 2012 i.e. end of RV season in China).

Table 1 presents the study groups and the epoch foreseen in the study.

**Table 1 Study groups and epochs foreseen in the study**

| Study group | Number of subjects | Age in weeks (MIN/Max) at Dose 1 | Epoch |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 – 16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedules: Two oral doses of the liquid HRV vaccine or placebo were to be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.
  - Subjects in each group were to receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 were to receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study were documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (Planned, N = 1625)
  - Group Placebo (Planned, N = 1625)

The treatment groups for the study are presented in Table 2.

**Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine were given concomitantly with liquid HRV Vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

- Treatment allocation: Randomised with balanced allocation (1:1).
- Blinding**:** Double-blind study.
- Blood Sampling: Blood samples were to be collected from two sub-cohorts of subjects.
  - Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).
  - Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples were to be collected from the subjects. Blood samples were to be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) reported after each dose of liquid HRV vaccine/placebo, using diary cards (was applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) reported after each dose of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (was applicable only for subjects in the immunogenicity sub-cohort 2).
- Unsolicited AEs were followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV vaccine/placebo.
- Recording of SAEs throughout the study period for all subjects.
  - for subjects who had completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs was done.
- Active follow-up for occurrence of GE* episodes was conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE was defined as diarrhoea with or without vomiting.
- For each GE episode occurring during the study period,
  - a GE diary card was completed daily until end of the GE symptoms.
  - a stool sample was collected as soon as possible after GE symptoms begin.
  - for subjects who had completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes was done.

- Parents/LARs of the subjects (including those subjects who had completed Visit 6 prior to the implementation of protocol amendment 2) were contacted to ask if their children would participate in the extended follow-up (Visit 7).
- An additional informed consent was taken for the extended follow-up.
- Type of study: self-contained.
- Data collection: eCRF.
- Final analysis was to be done as per protocol, when 40 severe RV GE episodes caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or at study conclusion, whichever was the earliest.

## 5.2. Study procedures

### 5.2.1. Outline of study procedures

Table 3 presents the list of study procedures.

**Table 3 List of study procedures**

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | Visit 7 |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | years 1 of age | April 2012[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | Efficacy follow up |
| Informed consent | ● | | | | | | |
| Re-consenting for Visit 7 follow-up | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | ○ | ○ | ○ | ○ | ○ | ○ |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approxi-mately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approxi-mately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approxi-mately 3mL: sub-cohort 2) | ● (Approxi-mately 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+ DTPa) | ● (OPV+ DTPa) | ● (DTPa) | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | Visit 7 |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | years 1 of age | April 2012[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | Efficacy follow up |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of unsolicited AEs within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | ○ | ○ | ○ | ○ | ○ | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

● used to indicate a study procedure that required documentation in the individual eCRF.
○ used to indicate a study procedure that did not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 were applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
[β]i.e. end of the RV season in China.

## 5.2.2. Intervals between study visits

Table 4 presents the intervals between study visits.

### Table 4 Intervals between study visits

| Interval | Optimal length of interval[1] | Maximum interval allowed[2] |
|---|---|---|
| 1 (Visit 1) → (Visit 2) | 30-48 days | 21-48 days |
| 2 (Visit 2) → (Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3) → (Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | 1 year of age± 2 weeks[γ] | 1 year of age ± 30 days |
| 6 (Visit 6) → (Visit 7) | 01 April 2012 to 30 April 2012[γ] | 01 April 2012 to 31 May 2012 |

[1]. Whenever possible the investigator arranged study visits within this interval
[2]. Subjects were not eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they made the study visit outside this interval
[γ] It was a defined time point for follow up visit in a range and not an interval.
Note: The date of the previous visit served as the reference date for intervals between study visits.

## 5.3. Selection of study population (Number of cases)

Target enrolment was 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated rate of non-evaluable subjects was 20%.

### 5.3.1. Inclusion criteria for enrolment (Selection of subjects)

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

- Subjects who the investigator believed that their parents/Legally Acceptable Representatives (LARs) could and would comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parent/LARs of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of 36 to 42 weeks inclusive.

### 5.3.2. Exclusion criteria (Selection of subjects)

The following criteria were checked at the time of study entry. If **ANY** exclusion criterion was applicable, the subject was not included in the study:

- Child in care.

  Refer to the glossary of terms for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone ≥ 0.5 mg/kg/day, or equivalent, inhaled and topical steroids were allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccines and ending 14 days after the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or would be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

- Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for Intussusception (IS).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness.
- History of confirmed RV GE.
- Acute disease and/or fever at the time of enrolment.
  - Fever was defined as temperature ≥37.1°C on axillary setting as defined by the Chinese authorities.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).
- GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

In addition to the criteria mentioned above, the following criteria were applicable to all subjects in the immunogenicity sub-cohort 2:

- History of diphtheria, tetanus and pertussis disease.
- History of seizures or progressive neurological disease.
- Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

### 5.3.3. Elimination criteria

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

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this meant prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and 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 the liquid HRV vaccine/placebo and ending 14 days after, with the exception of routine childhood vaccinations.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition likely to alter the immune response or are confirmed to have an immunodeficiency condition.

### 5.3.4. Contraindications to subsequent vaccination

***GSK Biologicals' liquid HRV vaccine or placebo:***

The following events constituted absolute contraindications to further administration of the liquid HRV vaccine or placebo. If any of these events occurred during the study, the subject did not receive additional doses of the vaccine but continued other study procedures at the discretion of the investigator.

- Hypersensitivity reaction following the administration of the liquid HRV vaccine or placebo.
- Intussusception (IS) and any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following events constituted contraindications to administration of liquid HRV vaccine and placebo at that point in time; if any of these events occurred at the time scheduled for vaccination, the subject was vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator.

- Acute disease at the time of vaccination. Acute disease was defined as the presence of a moderate or severe illness with or without fever. (Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.) All vaccines could be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness.
- GE within 7 days preceding the study vaccine administration.

***GSK Biologicals' DTPa vaccine:***

- DTPa vaccine was not administered to subjects with known hypersensitivity to any component of the vaccine or to subjects who showed signs of hypersensitivity after previous administration of DTPa vaccine.
- DTPa vaccine was contra-indicated if the child had experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with

pertussis containing vaccine. In these circumstances the vaccination course was continued with diphtheria and tetanus vaccine.

### 5.3.5. Warnings and precautions

*Warnings and precautions related to the liquid HRV vaccine*

The liquid HRV vaccine was under no circumstances to be injected.

*Warnings and precautions related to the DTPa*

It is good clinical practice that immunisation was preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of DTPa vaccine was to be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, was not a contra-indication.

If any of the following events occurred in temporal relation to receipt of DTPa, the decision to give subsequent doses of vaccine containing the pertussis component was carefully considered. There may have been circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events were not associated with permanent sequelae.

The following events were previously considered contra-indications for Diphtheria Tetanus whole cell Pertussis (DTPw) and are now considered general precautions:

- Temperature of ≥ 40.5°C within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

- In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it was better to defer pertussis (Pa) immunisation until the condition was corrected or stable. However, the decision to give pertussis vaccine was to be made on an individual basis after careful consideration of the risks and benefits.
- A history of febrile convulsions and a family history of convulsive fits did not constitute contra-indications.
- HIV infection was not considered as a contra-indication.
- As with all injectable vaccines, appropriate medical treatment was readily available in case of anaphylactic reactions followed by the administration of the vaccine. For

this reason, the vaccinee remained under medical supervision for 30 minutes after immunisation.

- As for all diphtheria, tetanus and pertussis vaccines, the vaccine was to be given deep intramuscularly and preferably at alternate injection sites.
- DTPa vaccine was to be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding could occur following an intramuscular administration to these subjects.
- DTPa vaccine was under no circumstances administered intravenously.
- The potential risk of apnoea and the need for respiratory monitoring for 48-72h was to be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination was high in this group of infants, vaccination was not withheld or delayed.

For warnings and precautions related to the OPV vaccines, please refer to the respective product labels/package inserts.

## 5.3.6. Subject completion and withdrawal

### 5.3.6.1. Subject completion

A subject who returned for the concluding visit in the protocol was considered to have completed the study.

### 5.3.6.2. Subject withdrawal

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

Withdrawals were not replaced.

#### *5.3.6.2.1. Subject withdrawal from the study*

From an analysis perspective, a ‘withdrawal’ from the study referred to any subject who did not come back for the concluding visit was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject was used for the analysis.

A subject was considered 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 documented in the eCRF. The investigator documented whether the decision to withdraw a subject from the study was made by the subject's parents/ LARs, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

#### *5.3.6.2.2. Subject withdrawal from investigational vaccine*

A 'withdrawal' from the investigational vaccine referred to 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 vaccine was not necessarily withdrawn from the study as further study procedures or follow-up could be performed (safety or immunogenicity) as planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine was documented on the Vaccine Administration screen of the eCRF. The investigator documented whether the decision to discontinue further vaccination/treatment was made by the subject's parents/ LARs or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-SAE.
- Other

## 5.4. Composition and administration of vaccines (Investigational Product)

### 5.4.1. Description of vaccines

Table 5 presents the formulation and presentation of study vaccines.

**Table 5 Study vaccines**

| Name of the Investigational Products: | liquid HRV vaccine | Placebo | DTPa | OPV |
|---|---|---|---|---|
| **Dosage form:** | Refer to Section 5.4.2 | Refer to Section 5.4.2 | Refer to Section 5.4.2 | Refer to Section 5.4.2 |
| **Source:** | RIX4414 HRV strain at least $10^{6.0}$ median $CCID_{50}$ Di-sodium Adipate 132.74 mg DMEM 2.26 mg Sucrose ***55%*** (w/w) water for injection q.s. as 1.5 mL **(Amended 14 August 2013)** | Di-sodium Adipate 132.74 mg DMEM 2.26 mg Sucrose ***55%*** (w/w) water for injection q.s. as 1.5 mL **(Amended 14 August 2013)** | Diphtheria toxoid ≥ 30 international units (IU) 25 Limits of flocculation (Lf) Tetanus toxoid ≥ 40 IU (10Lf) Pertussis toxoid 25 µg Filamentous haemagglutinin 25 µg Pertactin 8 µg Aluminium as salts 0.5 mg 2-phenoxyethanol ≤ 2.5 mg | per 0.1ml(2 drops) Total polio-virus, not less than 6.15lgCCID50 type1, not less than 6.0 lgCCID50 type2, not less than 5.0 lgCCID50 type3, not less than 5.5 lgCCID50 |
| **Lot number (BatchNumber)** | AROLA219B | PROLA008A | YC14B113AA | [20100202] |
| **Presentation (Specification)** | Liquid in a pre-filled oral applicator | Liquid in a pre-filled oral applicator | Turbid white suspension in a pre-filled syringe | liquid, oral |
| **Expiry date(Valid period)** | 30 September, 2012 | 31 October 2012 | 01 July,2012 | 01 February,2012 |

**Storage conditions:** Study vaccines were stored at the defined temperature range (i.e. +2 to +8°C). The storage temperature of the study vaccines was to be monitored daily while using validated temperature monitoring devices and the temperature measurements were to be recorded during working days, preferably at the same time of the day (e.g. at the beginning of the day). Freezing indication was to be continuously controlled by an appropriate device placed close to the study vaccines.

Any temperature deviation, i.e. temperature outside the defined range (i.e. +2 to +8°C), was to be reported to the Sponsor (i.e. Clinical Supplies Unit) as soon as detected. In case of temperature deviation between 0 and +2°C, the impacted study vaccines can still be administered, but the site must take adequate actions to go back to defined range +2 to +8°C and avoid re-occurrence of such a temperature deviation.

The liquid HRV vaccine and placebo used in this study were developed and manufactured by GSK Biologicals.

The DTPa vaccine used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 was developed and manufactured by GSK Biologicals.

The OPV vaccine used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 was developed and manufactured by Institute of Medical Biology Chinese Academy of Medical Sciences.

The Quality Control Standards and Requirements for the liquid HRV vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals were obtained.

The vaccines were labelled and packed according to applicable regulatory requirements.

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

### 5.4.2. Dosage and administration including administration route and basis for determining the administration route of study vaccines

The pre-filled oral applicator was shaken well before use. The product (vaccine or placebo) was then administered smoothly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration occurred in a quiet environment. Sufficient time was allowed for the baby to swallow the liquid vaccine solution, to avoid regurgitation or vomiting. If the subject regurgitated or vomited after study vaccine administration, no new study vaccine dose was administered. The subject continued to participate in the study. The oral vaccine intake characteristics (smooth vaccine intake, vaccine intake interrupted due to coughing or choking, regurgitation after vaccine intake, vomiting after vaccine intake) were recorded in the eCRF.

The vaccination regimen is summarised in Table 6.

**Table 6 Dosage and administration**

| Type of contact and time-point | Doses | Treatment Group | Vaccine | Route [1] | Site [2] | Side [3] |
|---|---|---|---|---|---|---|
| Visit 1 (day 0); Visit 2 (month 1) | 1 | Group HRV vaccine | liquid HRV vaccine | O | | |
| Visit 1 (day 0); Visit 2 (month 1) | 1 | Group Placebo | Placebo | O | | |
| Visit 2 (month 1); Visit 3 (month 2); Visit 4 (month 3) | 1 | Group HRV vaccine<br>Group Placebo | DTPa | IM | Ant T | L |
| Visit 1 (day 0); Visit 2 (month 1); Visit 3 (month 2) | 1 | Group HRV vaccine<br>Group Placebo | OPV | O | | |

[1]Oral (O)/ Intramuscular (IM)
[2]Thigh (T): Anterolateral (Ant)
[3]Left (L)

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

### 5.4.3. Treatment allocation and randomisation

The treatment allocation at the investigator site was performed using SBIR. The treatment numbers were allocated by kit. The randomisation algorithm used a minimisation procedure accounting for centre.

When SBIR was not available, SBIR user guide or the Study Procedures Manual (SPM) for specific instructions was used for reference.

After the eligibility of the subject was checked and ICF obtained, the site staff in charge of the vaccination accessed SBIR. Upon providing the subject identification number, the randomisation system used the minimisation algorithm to determine the treatment number to be used for the subject. Each treatment number was recorded in the eCRF on the Vaccine Administration screen.

#### 5.4.3.1. Randomisation of supplies

The randomisation was performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, a 6% over-randomisation of supplies was prepared.

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

### 5.4.4. Randomisation of subjects to assay sub-cohorts

Randomisation for all the sub-cohorts was done in parallel. Blood samples were collected from both the sub-cohorts of subjects:

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).
- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300).

### 5.4.5. Blinding

The study was conducted in a double-blind manner with respect to the liquid HRV vaccine and placebo. The parents/LARs of the subjects, the study personnel and the investigator were unaware of the study vaccine administered (liquid HRV vaccine/Placebo).

The level of blinding was maintained throughout the conduct of the trial, and only when the data was cleaned to an acceptable level of quality, appropriate personnel were unblinded or required in case of a SAE.

The final analysis was done by GSK.

## 5.5. Prior and concomitant medication /vaccinations

At each study visit/contact, the investigator questioned the subject's parents/LARs about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, were recorded in the eCRF. This also applied to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

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 was considered to be prophylactic when it was given in the absence of fever and any other symptom, to prevent fever from occurring (Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.).

Similarly, concomitant medication administered for the treatment of a SAE, at any time, was recorded on the SAE screens in the eCRF.

## 5.6. Laboratory assays and time points (Observational index and observational list for Laboratory testing)

**GE Stool analysis**

All stool sample assays were performed at the GSK Biologicals designated Clearstone laboratory (China) using standardised, validated procedures. All GE stool samples were analysed by Enzyme Linked Immunosorbent Assay (ELISA) for detection of RV antigen. If a stool sample tested positive for RV antigen, the sample was tested by Polymerase Chain Reaction (PCR) to determine the G and P genotype. If any RV G1 strain was detected in the stool specimens from Visit 1 up to study end, viral strain of the vaccine was differentiated from the wild type strain by sequence analysis or an equivalent approach.

**Serum analysis**

All serum sample assays were performed at GSK Biologicals designated NIFDC laboratory (China) using standardised, validated procedures. The back-up serum samples are stored at GSK Biologicals designated Clearstone laboratory (China). Serum anti-rotavirus IgA antibody concentrations were to be measured in all serum samples collected at Visit 1, Visit 3 and Visit 6 using ELISA. The assay cut-off was 20 U/mL. Antibodies to all antigens contained in the co-administered vaccines were to be measured at Visit 1 and Visit 5 (applicable only for subjects in the immunogenicity sub-cohort 2).

The laboratory assays to be performed are presented in Table 7.

**Table 7 Laboratory Assays**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | GSK Biologicals* |
| Serum | anti-diphtheria | ELISA** | NIFDC | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-tetanus | ELISA** | NIFDC | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-PT | ELISA** | NIFDC | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-FHA | ELISA** | NIFDC | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-PRN | ELISA** | NIFDC | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | NIFDC | $ED_{50}$† | 1:8 | GSK Biologicals* |

*GSK Biologicals laboratory or validated laboratory (NIFDC ) designated by GSK Biologicals in China.
**or Multiplex
ELISA = Enzyme Linked Immunosorbent Assay
NIFDC = National Institute for Food and Drug Control
U = Units; IU = International Units; EL.U = Elisa Units
†$ED_{50}$ = Estimated dose 50% is the seroprotective level.

Collected samples were to be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

## 5.7. Assessment of efficacy variables (Observational index and observational list for Laboratory testing)

Parents/LARs of all subjects were instructed to collect a stool sample from the subject if the subject developed GE symptoms (defined as diarrhoea with or without vomiting) during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks). A GE stool sample was to be collected as soon as possible after the illness began. A second GE stool sample was to be collected if the first sample was insufficient. A stool sample was collected for each GE episode. Two occurrences of diarrhoea were classified as separate episodes if there was a five day or more diarrhoea-free days between the episodes.

For each suspected GE episode that occurred during the study period, a GE diary card was completed by the parents/LARs daily until end of the GE symptoms. The completed diary cards were returned to the investigator at the following study visit. The investigator verified the returned completed GE diary cards and he/she or the study personnel transcribed the information into the appropriate sections of the eCRF, in English.

**Assessment of GE episodes**

Any GE episode (defined as diarrhoea with or without vomiting) that occurred starting from Visit 1 to study end was documented using the GE diary card. The following information was collected on the GE diary card during each GE episode: Axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given. The information collected on the GE diary card allowed the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

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

In the 20-point scoring system, points were assigned at GSK Biologicals according to the duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalisation (hospitalised subjects were considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 8.

**Table 8 The 20-point scoring system to determine the intensity of GE episodes reported during the study**

| Adverse Experience | Points |
|---|---|
| Duration of looser than normal stools (days) | |
| 1-4 | 1 |
| 5 | 2 |
| ≥ 6 | 3 |
| Maximum number of looser than normal stools /24 hours | |
| 1-3 | 1 |
| 4-5 | 2 |
| ≥ 6 | 3 |
| Duration of vomiting (days) | |
| 1 | 1 |
| 2 | 2 |
| ≥ 3 | 3 |
| Maximum number of episodes of vomiting/24 hours | |
| 1 | 1 |
| 2-4 | 2 |
| ≥ 5 | 3 |
| Fever∗<br>Axillary | |
| 36.6 – 37.9°C | 1 |
| 38.0 – 38.4°C | 2 |
| ≥ 38.5°C | 3 |
| Dehydration | |
| 1-5% | 2 |
| ≥ 6% | 3 |
| Treatment | |
| Rehydration | 1 |
| Hospitalisation | 2 |

∗The highest temperature recorded during the episode was scored.

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

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

## 5.8. Assessment of safety variables (Observational index and observational list for Symptoms and Signs)

### 5.8.1. Adverse events

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

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

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) were recorded in the medical history section of the subject's eCRF.

As a consistent method of soliciting AEs, the subject's parents/LARs were asked a non-leading question such as:

'*Did your child act differently or felt different in any way since receiving the vaccine or since the last visit?*'

When an AE/SAE occurred, it was the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator then recorded all relevant information regarding an AE/SAE on the eCRF or SAE Report screens as applicable. It was not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there could have been instances when copies of medical records for certain cases were requested by GSK Biologicals. In these instances, all subject identifiers were blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator attempted to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis was documented as the AE/SAE and not the individual signs/symptoms.

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that were judged by the investigator to be

clinically significant were recorded as AEs or SAEs if they met the definition of an AE, or of a SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened following the start of the study were reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that were associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that were present or detected at the start of the study and did not worsen, were not reported as AEs or SAEs.

The investigator exercised his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment was clinically significant.

#### 5.8.1.1. Assessment of intensity

Intensity of the following AEs was assessed as described in Table 9:

**Table 9 Intensity scales for solicited symptoms reported during the solicited follow-up period**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Fever* | | Recorded temperature in °C |
| Irritability/Fussiness | 0 | Behaviour was as usual |
| | 1 | Mild: Cried more than usual/no effect on normal activity |
| | 2 | Moderate: Cried more than usual/interfered with normal activity |
| | 3 | Severe: Crying that could not be comforted/prevented normal activity |
| Diarrhoea¶ | | Recorded the number of looser than normal stools /day |
| Vomiting§ | | Recorded the number of vomiting episodes/day |
| Loss of appetite | 0 | Appetite was as usual |
| | 1 | Mild: Ate lesser than usual/no effect on normal activity |
| | 2 | Moderate: Ate lesser than usual/interfered with normal activity |
| | 3 | Severe: Did not eat at all |
| Cough/runny nose | 0 | Normal |
| | 1 | Mild: Coughed/runny nose which was easily tolerated |
| | 2 | Moderate: Coughed/runny nose which interfered with daily activity |
| | 3 | Severe: Coughed/runny nose which prevented daily activity |
| Drowsiness | 0 | Behaviour was as usual |
| | 1 | Mild: Drowsiness was easily tolerated |
| | 2 | Moderate: Drowsiness that interfered with normal activity |
| | 3 | Severe: Drowsiness that prevented normal activity |
| Gastrointestinal symptoms (nausea,vomiting, diarrhoea and/or abdominal pain) | 0 | Gastrointestinal symptoms were normal |
| | 1 | Mild: Gastrointestinal symptoms that were easily tolerated |
| | 2 | Moderate: Gastrointestinal symptoms that interfered with normal activity |
| | 3 | Severe: Gastrointestinal symptoms that prevented normal activity |

*Fever was defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities
¶Diarrhoea was defined as passage of three or more, looser than normal stools within a day.
§Vomiting was defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day

**Table 10 Intensity scales used for diarrhoea, vomiting and fever reported during the solicited follow-up period**

| Adverse Experience | Intensity grade | Parameter |
|---|---|---|
| Diarrhoea | 0 | Normal (0 - 2 looser than normal stools/day) |
| | 1 | 3 looser than normal stools/day |
| | 2 | 4 - 5 looser than normal stools/day |
| | 3 | ≥ 6 looser than normal stools/day |
| Vomiting | 0 | Normal (no emesis) |
| | 1 | 1 episode of vomiting/day |
| | 2 | 2 episodes of vomiting/day |
| | 3 | ≥ 3 episodes of vomiting/day |
| Fever* | 0 | Axillary temperature < 37.1 °C |
| | 1 | Axillary temperature 37.1 °C - 37.5 °C |
| | 2 | Axillary temperature 37.6 °C - 39.0 °C |
| | 3 | Axillary temperature > 39.0 °C |
| Fever** | 0 | Axillary temperature < 37.5°C |
| | 1 | Axillary temperature ≥ 37.5 – ≤ 38.0°C |
| | 2 | Axillary temperature > 38.0 – ≤ 39.0°C |
| | 3 | Axillary temperature > 39.0°C |

*The maximum intensity of fever using the grading scale as defined by Chinese authorities.
**The maximum intensity of fever using the grading scale as defined by GSK Biologicals.

Intensity of the following solicited local AEs (DTPa vaccine) was assessed as described in Table 11.

**Table 11 Intensity scales for solicited local symptoms**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Pain at injection site | 0 | None |
| | 1 | Mild: Minor reaction to touch |
| | 2 | Moderate: Cried/protested on touch |
| | 3 | Severe: Cried when limb was moved/spontaneously painful |
| Redness at injection site | | Recorded greatest surface diameter in mm |
| Swelling at injection site | | Recorded greatest surface diameter in mm |

The maximum intensity of local injection site redness/swelling was scored at GSK Biologicals using the guidelines of AE grading set by Chinese Vaccine Clinical Research Guidelines as follows:

**Table 12 Intensity grades for redness/swelling**

| Intensity grade | Parameter |
|---|---|
| 0 | Absent |
| 1 | < 15 mm |
| 2 | ≥ 15 mm and ≤ 30 mm |
| 3 | > 30 mm |

The investigator assessed the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment was based on the investigator's clinical judgement.

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

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

An AE that was assessed as Grade 3 (severe) was not to be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs were assessed as Grade 3. An event was defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 5.8.2.

#### 5.8.1.2. Assessment of causality

The investigator was obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator used clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product were considered and investigated. The investigator also consulted the Investigator Brochure in the determination of his/her assessment.

There could have been situations when a SAE had occurred and the investigator had minimal information to include in the initial report to GSK Biologicals. However, it was very important that the investigator always made an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator could change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment was one of the criteria used when determining regulatory reporting requirements.

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

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

*Was there a reasonable possibility that the AE may have been caused by the liquid HRV vaccine?*

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

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

Non-serious and serious AEs were evaluated as two distinct events. If an event met criteria to be determined 'serious' (see Section 5.8.2 for definition of SAE), additional examinations/tests were performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors included:

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

#### 5.8.1.3. Assessment of outcomes

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study was assessed as:

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

### 5.8.2. Serious adverse events

#### 5.8.2.1. Definition of a serious adverse event

A SAE was any untoward medical occurrence that:

a. resulted in death.

b. was life-threatening.

NB: 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 could have caused death, had it been more severe.

c. Required hospitalisation or prolongation of existing hospitalisation.

NB: In general, hospitalisation signified that the subject had been admitted 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 also considered AEs. If a complication prolonged hospitalisation or fulfilled any other serious criteria, the event was considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE was considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline was NOT considered an AE.

d. Resulted in disability/incapacity,

NB: 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 like illness, and accidental trauma (e.g. sprained ankle) which could have interfered or prevented everyday life functions but did not constitute a substantial disruption.

Medical or scientific judgement was exercised in deciding whether reporting was appropriate in other situations, such as important medical events that were not immediately life-threatening or resulted in death or hospitalisation but could have jeopardised the subject or could have require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These were also considered serious. Examples of such events were invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that did not result in hospitalisation.

## 5.9. Statistical methods (Statistical Processing Scheme)

The statistical analyses were performed using the SDD (i.e **S**AS **D**rug and **D**evelopment) web portal version 3.5 and SAS version Proc stat xact 8.1.

The study endpoints considered for analyses presented in this study report are listed below. Immunogenicity endpoints will be presented in a separate annex report.

### 5.9.1. Primary outcome/Efficacy Variable

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

### 5.9.2. Secondary Outcome/Efficacy Variables

***Efficacy***

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

***Reactogenicity and Safety***

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

### 5.9.3. Determination of sample size

Target enrolment was 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated rate of non evaluable subjects was 20%.

Considering a 1:1 randomisation ratio and various incidence rates, Table 13 provides the power to observe a lower limit of the 95% CI for vaccine efficacy to be above 0% and 10%.

For a 2% attack rate of RV GE in the placebo group from 2 weeks post Dose 2 to end of efficacy follow-up period, and if the vaccine efficacy was 80%, the study had 95.8% power to observe a 95% CI for the vaccine efficacy that could be above 10%. It was expected to observe a total of 40 severe RV GE cases during the efficacy follow-up period in the total vaccinated cohort.

**Table 13 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 2600 evaluable subjects – 1300 subjects in HRV group and 1300 subject in the placebo group, power based on 1,000 simulations using Proc StatXact)**

| Incidence rate in the Placebo for severe RV GE | VE (%) | Power to have a lower limit of the 95%CI on VE ≥ 0% | Power to have a lower limit of the 95%CI on VE ≥ 10% |
|---|---|---|---|
| 1% | 70 | 54.5% | 44.2% |
| | 80 | 69.6% | 60.8% |
| 1.5% | 70 | 74.4% | 65.1% |
| | 80 | 87.8% | 82.7% |
| 2%* | 70 | 85.1% | 77.2% |
| | 80** | 97.6% | 95.8% |
| 2.5% | 70 | 92.7% | 87.8% |
| | 80 | 99.4% | 98.6% |
| 3% | 70 | 96.4% | 92.3% |
| | 80 | 99.4% | 99.3% |

*anticipated rate in the Placebo for severe RV GE.
VE - Vaccine Efficacy. CI-Confidence Interval
**anticipated vaccine efficacy
Attack Rate (AR) = 1.5% [1.0%; 2.3%], VE = 95.3% [73.1%;99.9%].

### 5.9.4. Study cohorts /data sets analyzed

#### 5.9.4.1. Total vaccinated cohort

The total vaccinated cohort included all subjects with at least one dose of the liquid HRV vaccine or placebo administration documented:

- A safety analysis based on the total vaccinated cohort included all vaccinated subjects,
- An efficacy analysis based on the total vaccinated cohort included all vaccinated subjects for whom efficacy follow-up data was available.

#### 5.9.4.2. ATP cohort for analysis of safety

The ATP cohort for safety included all vaccinated subjects:

- who received at least one dose of HRV vaccine/Placebo according to their random assignment.
- for whom the randomisation code was not broken, who did not received a vaccine forbidden by or not specified in the protocol.

#### 5.9.4.3. ATP cohort for analysis of efficacy

The ATP cohort for efficacy included all subjects from ATP the cohort for safety.

- 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 received 2 doses of the liquid HRV vaccine or placebo,
- who have entered the efficacy surveillance period:
  - have follow-up beyond 2 weeks post Dose 2 of study vaccination
  - who have no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks post Dose 2 of liquid HRV vaccine or placebo.

## 5.10. According-to-protocol cohort for analysis of efficacy for second year follow-up

- The ATP cohort for efficacy for second year follow-up will include all subjects from ATP cohort for efficacy, who have follow-up beyond visit 6 (year 1).

### 5.10.1. Derived and transformed data

**Demography**

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

**Efficacy**

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

The subjects, who had completed Visit 6 and had not given their consent to participate in the extension follow-up, were considered as dropouts from the study. The ATP cohort for the analysis of efficacy included all the subjects who had satisfied the points mentioned in the section 5.9.4.3.

**Safety/Reactogenicity**

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

### 5.10.2. Analysis of demographics (Analysis)

The mean, range and standard deviation of height in cm and weight in kg at Visit 1 were calculated per group and overall. The racial and gender composition was presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo was calculated per group and overall. The distribution of subjects enrolled among the study centres was tabulated as a whole and per group. The percentages of subjects who received concomitant and intercurrent vaccinations were tabulated by group.

### 5.10.3. Analysis of efficacy (Analysis)

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

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

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

- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to each non-G1 type during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe all cause GE during the efficacy follow-up period.

Vaccine efficacy was also derived from a Cox regression model on the time to first event with censoring for subjects without an event as an additional supportive and exploratory analysis.

Vaccine efficacy analysis was also performed on the data collected from 2 weeks post Dose 2 of HRV vaccine /placebo up to visit 6. This was presented as an additional supportive analysis.

- The primary objective was considered met if the lower limit of the 95% confidence interval on vaccine efficacy (conditional method) for the HRV group against severe RVGE caused wild-type RV strains during the efficacy follow-up period was ≥ 10.

Vaccine efficacy, derived from a Cox regression model on the time to first event with censoring at the database lock for subjects without event. The model included the group as fixed effect. This was performed as an exploratory/supportive analysis. [Kalbfleisch, 2002]

- Incidence rate in a group (P) was computed as the number of subjects reporting at least one event (n)/total follow-up time to a first event censored at visit 7 (T). The associated 95% CI's were obtained considering that n follows a Poisson distribution with P*T parameter.
- The number of events prevented by 100 vaccinated infant-years was obtained from 100 times the difference in the incidence rate. The associated CI was derived using the method proposed by G.Y. Zou and A. Donner [Zou, 2008]. This was performed as an exploratory/supportive analysis.
- An exploratory/supportive analysis of vaccine efficacy by serostatus of subjects against rota virus IgA antibody at Visit 3 will be performed.

The same analysis was also performed on Total Vaccinated Cohort from Dose 1 to study end and from Dose 1 to Visit 6.

An exploratory analysis of efficacy was performed on the efficacy data collected between Visit 6 to visit 7 on the subjects who have follow-up beyond Visit 6 (ATP cohort for efficacy for second year follow-up).

### 5.10.3.1. Analysis of Safety (Analysis)

***Analysis of Safety (solicited AEs):***

The analysis of safety was based on the TVC. As the percentage of enrolled subjects excluded from the ATP cohort for safety was lower than 5% in both groups, no analysis based on the ATP cohort was performed.

Note: Intensity of fever was assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale was performed separately.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each dose, for overall doses and per subject. The same calculations will be performed for any grade 3 (solicited or unsolicited) symptoms and for any (solicited or unsolicited) symptom related to vaccination.

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

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects with at least one local AE (solicited and unsolicited) after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination were tabulated with exact 95% CI. The same calculations were performed for any grade 3 (solicited or unsolicited) symptoms, grade 3 related symptoms and for any symptoms requiring medical attention.

- The percentage of subjects reporting each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa during the 8-day (Days 0–7) follow-up period with exact 95% CI were tabulated.

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation were done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

**For all subjects:**

The incidence, with exact 95% CI, of each individual solicited general symptom common to both the sub-cohorts, will be calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

- Occurrence of fever was reported per 0.5°C cumulative temperature increments

The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to MedDRA. Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI was tabulated by group, and by preferred term. Similar tabulation was done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period was tabulated by type of medication, with exact 95% CI. Similar tabulations were done for subjects who receive concomitant medication during the study period.

SAEs reported during the study period (i.e. from first vaccine dose till study end) were described in detail.

There was a retrospective follow-up on SAEs for subjects who had already completed Visit 6 prior to the implementation of protocol amendment 2 and this was documented in the eCRF.

### 5.10.4. Sequence of analyses

Final analysis was to be done as per protocol, when 40 severe RV GE episodes caused by the circulating wild-type RV strains was reached during the efficacy follow-up period or at study conclusion, whichever was the earliest. Interim analysis

No interim analysis was planned for this study.

## 5.11. Data quality assurance

To ensure that the study procedures conformed across all investigator sites, the protocol, electronic case report form and safety reporting were reviewed with the investigator(s) and his/her/their personnel responsible for the conduct of the study by the Company representative(s) prior to study start. An investigator meeting was held prior to the study start.

**Independent Audit statement:**

- This study was subject to audit by GSK's Clinical Development Quality Assurance (CDQA) at the centre number [redacted] on 26th-27th June 2010.

## 5.12. Changes in the conduct of the study or planned analyses (Modification in process of study)

### 5.12.1. Protocol amendments

**Protocol Amendment 1 (02 September 2010):**

The following changes were reflected in Protocol amendment 1: 6% over-randomisation of supplies, parallel randomisation of subjects to assay sub-cohorts and change in time periods for administration of medications/products that could have led to the elimination of a subject from ATP analyses.

**Protocol Amendment 2 (05 August 2011):**

The protocol was amended again on 05 August 2011 to reflect the extension of the efficacy follow-up period until the end of the second RV season in China. Based on the preliminary review of GE episodes reported prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seemed lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up was extended until approximately April 2012 (i.e. end of RV season in China).

### 5.12.2. Other changes

This study was conducted according to the protocol.

Analyses were performed as planned in the protocol and/or SAP except for the following changes:

- The cohort "ATP cohort for efficacy – Extended follow-up" will be referred to as "ATP cohort for efficacy for second year follow up" in the report tables.
- Table for VE by RV types was generated for the data between Visit 6 & Visit 7 on ATP cohort for efficacy for second year follow up.
- Tables on all cause of GE, Severe GE & Hospitalized due to RVGE was generated for Dose 1 up to before Dose 2 and Dose 1 up to 2 weeks post-Dose 2 on TVC.
- Table for concomitant medication was generated on sub-cohort 2 from Day 0 to Day 7 and on pooled sub-cohorts for entire study period.
- Percentage of subjects reporting unsolicited symptoms during the entire study period was generated on TVC.
- Titles for some of the tables was changed from "subjects belonging to sub cohort 1 and 3" to "except immunogenicity sub cohort 2" and from "subjects belonging to immunogenicity sub cohort 2" to "except immunogenicity sub cohorts".

This report presents the efficacy, safety and reactogenicity results of the subjects after study completion. Immunogenicity results are not yet available and will be presented in an annex report.

- The final analysis presents the efficacy, safety and reactogenicity data collected from Dose 1 of HRV/Placebo up to Visit 7 and this analysis was run by a GSK statistician. All individual data listings except for immunogenicity data are presented along with this reported.
- An annex report will present the immunogenicity data collected during the study. This analysis will present the individual data listings for immunogenicity data.

# 6. STUDY POPULATION RESULTS (STUDY RESULTS)

## 6.1. Study dates

The first subject was enrolled in the study on 29 August 2010 and the last study visit was on 12 May 2012.

## 6.2. Subject eligibility and attrition from the study

### 6.2.1. Number of subjects

The number of subjects enrolled in the study by centre is presented in the following tables:

Table 14 Number of subjects by centre (Total vaccinated cohort)

Table 15 Subjects unblinded before database lock (13AUG2012) (Total vaccinated cohort)

Table 16 Number of subjects in the sub-cohorts (Total vaccinated cohort)

### 6.2.2. Study completion and withdrawal from study

The reasons for withdrawal are presented in the following table:

Table 17 Number of subjects entered, completed and withdrawn with reason for withdrawal till Visit 7 (Total vaccinated cohort)

### 6.2.3. Protocol deviations

The deviations are presented in the following table:

Table 18 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

Table 19 Protocol deviations not leading to exclusion of subjects or their data from analysis

## 6.3. Demographic characteristics

### 6.3.1. ATP cohort for efficacy

The demographic characteristics and the vital signs are presented in the following tables:



### 6.3.2. Total Vaccinated cohort

The demographic characteristics are presented in the following table:



## 6.4. Concomitant and Intercurrent Vaccinations

The summary of co-administered vaccines and vaccinations other than the investigational product are presented in the following tables:

# 7. EFFICACY RESULTS

## 7.1. Data sets analyzed

Analysis of efficacy was performed on the ATP cohort for efficacy (primary analysis) and the total vaccinated cohort. See Section 5.9.4 for the definition of the cohorts identified for analyses and Section 6.2 eligibility for analyses.

## 7.2. According-to-protocol analysis for efficacy

### 7.2.1. Characterization of GE episodes

The results are detailed in the following tables and figures:



- A total of 728 subjects (46.2%) from the HRV group and 759 subjects (48.3%) from the placebo group had reported at least one GE episode (Table 36).
- Of all the GE episodes that were tested, rotavirus was detected in 70 GE episodes (4.4%) in the HRV group and 167 GE episodes (10.6%) in the placebo group (Table 36).
- Severe RV GE was reported for 21 subjects (1.3%) and for 75 subjects (4.8%) in the HRV group and placebo group, respectively (Table 36).

- When the GE and RV GE episodes were scored using the 20-point Vesikari scale, the distribution of the reported GE episodes among mild, moderate and severe intensity was similar in both groups. There were more RV GE episodes rated as severe (Vesikari scale ≥11) in the placebo group [75 RV GE episodes (44.1%) as compared to 21 (30%) RV GE episodes in the HRV group] (Table 37).

The percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 39 Percentage of subjects with RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

Table 40 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 41 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

Table 42 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

- Among the RV GE episodes, G1P[8] (27.1% in the HRV group and 20.0% in the placebo group) and G2P[4] (55.7% in the HRV group and 57.0% in the placebo group) were the most common RV types circulating during the efficacy period (Table 41).
- Among the severe RV GE episodes, G1P[8] (38.1% in the HRV group and 24.0% in the placebo group) and G2P[4] (47.6% in the HRV group and 49.3% in the placebo group) were the most common RV types circulating during the efficacy follow-up period (Table 42).

Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:

Table 43 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 44 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G1WT type (ATP cohort for efficacy)

Table 45 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G2 type (ATP cohort for efficacy)

In general, clinical RV GE episodes were more severe (based on Vesikari scale) and had longer duration of symptoms in the placebo group when compared to the HRV group (Table 43 to Table 49).

The duration of efficacy follow-up is presented in the following table and figures:



- The mean duration of efficacy follow-up from 2 weeks post Dose 2 up to Visit 7 was 1.34 years in the HRV group and 1.33 years for the placebo group.

### 7.2.2. Vaccine efficacy from 2 weeks after Dose 2 up to Visit 7

#### 7.2.2.1. Vaccine efficacy against severe RV GE (Primary Endpoint)

The results are detailed in the following tables and figures:

Table 51 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 52 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Figure 4 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV was 72.0% [95% CI: 54.1%; 83.6%]. Severe RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (1.3% versus 4.8%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 51). The primary objective of the study was met since the lower limit of the 95% CI on VE was above 10% (pre-specified criteria for the primary efficacy objective).
- Vaccine efficacy based on Cox proportional hazard model against severe RV GE was 72.7% [95% CI: 55.8%; 83.2%]. Per 100 infant years, 2.7 episodes of severe RV GE can be prevented if the subjects are vaccinated with the liquid HRV vaccine (Table 58 and Table 59).

#### 7.2.2.2. Vaccine efficacy against any RV GE

The results are detailed in the following table and figure:

Table 53 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Figure 5 The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.1% [95% CI: 44.3%; 68.8%]. RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (4.4% versus 10.6%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 53).

- Vaccine efficacy based on Cox proportional hazard model against RV GE was 60% [95% CI: 47.1%; 69.7%]. Per 100 infant years, 5.1 episodes of any RV GE could be

prevented by vaccinating the subjects with the liquid HRV vaccine (Table 58 and Table 59).

#### 7.2.2.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figures:

Table 54 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)

Table 55 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)

Figure 6 The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Figure 7 The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against severe RV GE caused by G1 and non-G1 RV GE strains was 64.0% [95% CI: 20.4%; 85.2%] and 77.8% [95% CI: 58.0%; 89.2%], respectively (Table 54).
- Vaccine efficacy against severe RV GE caused by wild type G1P[8] was 60.1% [95% CI: 5.3%; 84.8% ]. Among the subjects reported for severe RV GE episodes, wild type G1P[8] was identified for 0.5% subjects in the HRV group and 1.3% subjects in the placebo group (Table 55).
- Vaccine efficacy against severe RV GE caused by G2P[4] was 72.5% [95% CI: 45.5%; 87.3%]. Among the subjects reported for severe RV GE episodes, G2P[4] was identified for 0.7% subjects in the HRV group and 2.5% subjects in the placebo group (Table 55).

**Vaccine efficacy against any RV GE by RV type**

Table 56 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)

Table 57 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)

Table 58 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against any RV GE caused by wild type G1P[8] was 47.4% [95% CI: 7.4%; 71%]. Among the subjects reported for any RV GE episodes caused by G1 types, wild type G1P[8] was identified for 1.3% subjects in the HRV group and 2.4% subjects in the placebo group (Table 57).
- Vaccine efficacy against any RV GE caused by G2P[4] was 58.9% [95% CI: 40.5%; 72.0%]. Among the subjects reported for any RV GE episodes caused by non-G1 types, G2P[4] was identified for 2.7% subjects in the HRV group and 6.5% subjects in the placebo group (Table 57).

#### 7.2.2.4. Vaccine efficacy against hospitalisation due to RV GE



- Vaccine efficacy against RV GE caused by circulating wild-type RV that required hospitalization was 81.0% [95% CI: 43.6%; 95.3%]. Fewer subjects in the HRV group required hospitalization following an episode of RV GE as compared to the placebo group (0.3% versus 1.3%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 60).
- Vaccine efficacy against RV GE leading to hospitalization or requiring rehydration therapy was 66.4% [95% CI: 49.6%; 78.1%]. Fewer subjects in the HRV group were hospitalized and/or required rehydration therapy following an episode of RV GE as compared to the placebo group (2.1% versus 6.2%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7 (Table 61).

#### 7.2.2.5. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 62 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 63 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 64 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

Table 65 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

- Vaccine efficacy against all cause GE was 4.2% [95% CI: -6.2%; 13.6%]. All cause GE episodes occurred at a similar rate in the HRV group and placebo group (46.2% versus 48.3%, p-value 0.422) from 2 weeks post Dose 2 up to the Visit 7 (Table 62).
- Vaccine efficacy against all cause severe GE was 9.3% [95% CI: -11.1%; 26.0%]. All cause severe GE episodes occurred at a similar rate in the HRV group and placebo group (11.9% versus 13.1%, p-value: 0.357) from 2 weeks post Dose 2 up to the Visit 7 (Table 63).
- Vaccine efficacy against all cause GE that required hospitalization was 41.2% [95% CI: 13.1%; 60.6%]. Fewer subjects in the HRV group required hospitalization following an episode of all cause GE as compared to the placebo group (2.7% versus 4.6%, p-value 0.007) from 2 weeks post Dose 2 up to the Visit 7 (Table 64).

### 7.2.3. Vaccine efficacy results from 2 weeks after Dose 2 up to Visit 6

The results are detailed in the following tables and figures:

Table 66 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 67 Number of GE episodes reported from 2 weeks after Dose 2 up to Visit 6 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

Table 68 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

The percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

The number of RV GE and severe RV GE episodes by G P type are presented in the following tables:



Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:



The duration of efficacy follow-up is presented in the following table and figures:

#### 7.2.3.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables and figures:



#### 7.2.3.2. Vaccine efficacy against any RV GE

The results are detailed in the following table and figure:



- Fewer subjects in the HRV group reported any RV GE episode caused by the circulating wild-type RV compared to the placebo group (1.7% versus 5.7%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 6.
- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 70% [95% CI: 53.5%; 81.3%] (Table 82).

#### 7.2.3.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figure:

**Vaccine efficacy against any RV GE by RV type**

The results are detailed in the following tables and figures:



#### 7.2.3.4. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:

### 7.2.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 91 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 92 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 93 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

Table 94 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

### 7.2.5. Characterization of GE episodes after Visit 6 up to Visit 7

The results are detailed in the following tables:

Table 95 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

Table 96 Number of GE episodes reported from Visit 6 up to Visit 7 by severity using the 20-point Vesikari scale (ATP cohort for efficacy - second year follow-up period)

Table 97 Percentage of GE episodes with no available stool results from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 98 Percentage of subjects with RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

Table 99 Percentage of subjects with severe RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 100 Number of RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

Table 101 Number of severe RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

The duration of efficacy follow-up is presented in the following table:

Table 102 Duration (in years) of efficacy follow-up period - from Visit 6 up to Visit 7 (ATP cohort for efficacy - second year follow-up period)

## 7.2.6. Vaccine efficacy from after Visit 6 up to Visit 7

### 7.2.6.1. Vaccine efficacy against severe RV GE

The results are detailed in the following table:

Table 103 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

### 7.2.6.2. Vaccine efficacy against any RV GE

The results are detailed in the following table:

Table 104 Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following table:

Table 105 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)

**Vaccine efficacy against any RV GE by RV type**

The results are detailed in the following table:

Table 106 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)

#### 7.2.6.3. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:

Table 107 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

#### 7.2.6.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 108 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Visit 6 up to Visit 7

Table 109 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Visit 6 up to Visit 7

Table 110 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)

## 7.3. Total vaccinated cohort analysis

### 7.3.1. Characterization of GE episodes from Dose 1 to Visit 7

The results are detailed in the following tables and figures:

Table 111 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 up to Visit 7 (Total vaccinated cohort)

Table 112 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to Visit 7 (Total vaccinated cohort)

Table 113 Number of GE episodes reported from Dose 1 up to Visit 7 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

Table 114 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 7 (Total vaccinated cohort)

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 115 Percentage of subjects with RV GE episodes from Dose 1 up to Visit 7 by G and P type (Total vaccinated cohort)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:



Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:



The duration of efficacy follow-up is presented in the following table and figures:

### 7.3.2. Vaccine efficacy during the period from Dose 1 up to Visit 7

#### 7.3.2.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables and figures:

Table 127 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

Table 128 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

Figure 24 The Kaplan Meier curve for severe RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)

Figure 25 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from Dose 1 up to Visit 7 (Total vaccinated cohort)

#### 7.3.2.2. Vaccine efficacy against any RV GE

The results are detailed in the following tables and figure:

Table 129 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

Figure 26 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)

#### 7.3.2.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figures:

Table 130 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by RV type (Total vaccinated cohort)

Table 131 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by combination of G and P types (Total vaccinated cohort)

Figure 27 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 7 (Total vaccinated cohort)

**Vaccine efficacy against any RV GE by RV type**



#### 7.3.2.4. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:



#### 7.3.2.5. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

### 7.3.3. Characterization of GE episodes from Dose 1 up to Visit 6

The results are detailed in the following tables and figures:



Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:



The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:



Characteristics of RV GE episodes based on the Vesikari scale are presented in the following tables:

The duration of efficacy follow-up is presented in the following table and figures:



### 7.3.4. Vaccine efficacy during the period from Dose 1 up to Visit 6

#### 7.3.4.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables and figures:

#### 7.3.4.2. Vaccine efficacy against any RV GE

The results are detailed in the following tables and figure:

Table 158 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)

Figure 36 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 6 (Total vaccinated cohort)

#### 7.3.4.3. Vaccine efficacy against circulating RV types

**Vaccine efficacy against severe RV GE by RV type**

The results are detailed in the following tables and figures:

Table 159 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)

Table 160 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)

**Vaccine efficacy against any RV GE by RV type**

Table 161 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)

Table 162 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)

Table 163 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from Dose 1 up to Visit 6 (Total vaccinated cohort)

Table 164 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 6 by Cox method (Total vaccinated cohort)

Figure 37 The Kaplan Meier curve for any RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)

Figure 38 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 6 (Total vaccinated cohort)

Figure 39 The Kaplan Meier curve for severe RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)

#### 7.3.4.4. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following tables:



#### 7.3.4.5. Vaccine efficacy against all cause GE

The results are detailed in the following tables:



### 7.3.5. Characterization of GE episodes from Dose 1 up to before Dose 2

The results are detailed in the following tables:

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 174 Percentage of subjects with RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

Table 175 Percentage of subjects with severe RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

No record exists for the above mentioned table.

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 176 Number of RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

Table 177 Number of severe RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

No record exists for the above mentioned table.

The duration of efficacy follow-up is presented in the following table:

Table 178 Duration (in years) of efficacy follow-up period - Dose 1 up to before Dose 2 (Total vaccinated cohort)

## 7.3.6. Vaccine efficacy during the period from Dose 1 before Dose 2

### 7.3.6.1. Vaccine efficacy against severe RV GE

The results are detailed in the following tables:

Table 179 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

No record exists for the above mentioned table.

### 7.3.6.2. Vaccine efficacy against any RV GE

The results are detailed in the following table:

Table 180 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

#### 7.3.6.3. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following table:

Table 181 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

No record exists for the above mentioned table.

#### 7.3.6.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 182 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

Table 183 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)

### 7.3.7. Characterization of GE episodes from Dose 1 up to 2 weeks post dose 2

The results are detailed in the following tables:

Table 184 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort )

Table 185 Number of GE episodes reported from Dose 1 up to 2 weeks post-Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

Table 186 Percentage of GE episodes with no available stool results from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

Percentage of subjects reported for RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 187 Percentage of subjects with RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

Table 188 Percentage of subjects with severe RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

Table 189 Number of RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

The number of RV GE and severe RV GE episodes by G and P type are presented in the following tables:

Table 190 Number of severe RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

The duration of efficacy follow-up is presented in the following table:

Table 191 Duration (in years) of efficacy follow-up period from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

## 7.3.8. Vaccine efficacy during the period from Dose 1 up to 2 weeks post dose 2

### 7.3.8.1. Vaccine efficacy against severe RV GE

The results are detailed in the following table:

Table 192 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

### 7.3.8.2. Vaccine efficacy against any RV GE

The results are detailed in the following table:

Table 193 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

### 7.3.8.3. Vaccine efficacy against hospitalisation due to RV

The results are detailed in the following table:

Table 194 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

No record exists for the above mentioned table.

### 7.3.8.4. Vaccine efficacy against all cause GE

The results are detailed in the following tables:

Table 195 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

## 7.4. Efficacy summary

- Vaccine efficacy against severe RV GE caused by circulating wild-type RV was 72.0% [95% CI: 54.1%; 83.6%]. Severe RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (1.3% versus 4.8%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7. The primary objective of the study was met since the lower limit of the 95% CI on vaccine efficacy was above 10% (pre-specified criteria for the primary efficacy objective).
- Vaccine efficacy against any RV GE caused by the circulating wild-type RV was 58.1% [95% CI: 44.3%; 68.8%]. RV GE caused by circulating wild-type RV was reported by significantly fewer subjects in the HRV group compared to the placebo group (4.4% versus 10.6%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating wild type G1 was 52.2% [95% CI: 19.0%; 72.6%] and 64.0% [95% CI: 20.4%; 85.2%], respectively. Vaccine efficacy against severe RV GE caused by circulating wild type G1P[8] was 60.1% [95% CI: 5.3%; 84.8%]. Vaccine efficacy against any RV GE caused by G1P[8] was 47.4% [95% CI: 7.4%; 71%, p-value 0.024]. Fewer subjects in the HRV group reported any and severe RV GE caused by circulating wild-type G1 compared to the placebo group (1.4% and 0.6% versus 2.9% and 1.6% , respectively, p-value 0.005 and 0.009) from 2 weeks post-Dose 2 up to the Visit 7.
- Vaccine efficacy against any and severe RV GE caused by circulating non-G1 type was 62.1% [95% CI: 46.9%; 73.3%] and 77.8% [95% CI: 58.0%; 89.2%], respectively. Fewer subjects in the HRV group reported any and severe non-G1 type RV GE episode compared to the placebo group (3.1% and 0.8% versus 8.2% and 3.4%, respectively, p-value <0.001 for both) from 2 weeks post-Dose 2 up to the Visit 7. Vaccine efficacy against any RV GE caused by G2P[4] was 58.9% [95% CI: 40.5%; 72.0%, p-value <0.001].Vaccine efficacy against severe RV GE caused by G2P[4] was 72.5% [95% CI: 45.5%; 87.3%].
- Vaccine efficacy against RV GE caused by circulating wild-type RV that required hospitalization was 81% [95% CI: 43.6%; 95.3%]. Fewer subjects in the HRV group required hospitalization following an episode of RV GE as compared to the placebo group (0.3% versus 1.3%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against RV GE leading to hospitalization or requiring rehydration therapy was 66.4% [95% CI: 49.6%; 78.1%]. Fewer subjects in the HRV group were hospitalized and/or required rehydration therapy following an episode of RV GE as compared to the placebo group (2.1% versus 6.2%, p-value <0.001) from 2 weeks post Dose 2 up to the Visit 7.

- Vaccine efficacy against all cause GE was 4.2% [95% CI: -6.2%; 13.6%]. All cause GE episodes reported for subjects in HRV group and placebo group was similar (46.2% versus 48.3%, p-value 0.422) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause severe GE was 9.3% [95% CI: -11.1%; 26.0%]. All cause severe GE episodes for subjects in HRV group and placebo group was similar (11.92% versus 13.1%, p-value: 0.357) from 2 weeks post Dose 2 up to the Visit 7.
- Vaccine efficacy against all cause GE that required hospitalization was 41.2% [95% CI: 13.1%; 60.6%]. Fewer subjects in the HRV group required hospitalization following an episode of all cause GE as compared to the placebo group (2.7% versus 4.6%, p-value 0.007) from 2 weeks post Dose 2 up to the Visit 7.

# 8. SAFETY RESULTS

## 8.1. Data sets analyzed

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

## 8.2. Total vaccinated cohort analysis

The results are detailed in the following tables:

Table 197 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort)

Table 198 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort- except immunogenicity sub-cohorts)

Table 199 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort- Immunogenicity sub-cohort 2)

Table 200 Compliance in returning symptom sheets (Total vaccinated cohort- except immunogenicity sub cohort 2)

Table 201 Compliance in returning symptom sheets (Total vaccinated cohort- Immunogenicity sub cohort 2)

- The majority (at least 95.8%) of the subjects in the HRV group and placebo group received both doses (Table 197).
- Symptom sheets were completed for at least 98% of the doses in both groups (Table 200 and Table 201).

### 8.2.1. Overall incidence of adverse events

The results are detailed in the following tables:

All subjects except immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any AEs (solicited or unsolicited) based on GSK scale for fever (44.2% in the HRV group and 47.3% in the placebo group) and Chinese scale for fever (51.5% in the HRV group and 53.8% in the placebo group) was similar in both groups. There was no increase in the incidence of AEs (solicited or unsolicited) from Dose 1 to Dose 2 of the HRV vaccine (Table 202 and Table 203).
- The incidence of AEs (solicited or unsolicited) rated as grade "3" in intensity and those assessed as causally related to vaccination were also similar in both groups (Table 204 and Table 205).

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any general symptoms (solicited or unsolicited) was 52.9% [95% CI 44.7%; 61.1%] subjects in the HRV group and 50.3% [95% CI: 42.1%; 58.5%] subjects in the placebo group. Any general symptoms (solicited or unsolicited) were reported for 42.5% [95% CI: 34.5%; 50.7%] and 30.0% [95% CI: 22.8%; 38.0%] subjects after the first and second dose of HRV vaccine, respectively. No more than 16.0% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine (Table 207).
- During the 8-day follow-up period (Day 0 to Day 7), any general symptoms (solicited or unsolicited) rated as grade "3" in intensity and causally related to vaccination were reported for 2.6% [95% CI: 0.7%; 6.6%] subjects in the HRV group and 2.0% [95% CI: 0.4%; 5.6%] subjects in the placebo group. No more than 1.3% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade "3" in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine (Table 210).
- During the 8-day follow-up period (Day 0 to Day 7), any AEs (solicited or unsolicited) requiring medical attention were reported for 12.4% [95% CI: 7.6%; 18.7%] subjects in the HRV group and 11.1% [95% CI: 6.6%; 17.2%] subjects in the placebo group (Table 211).

### 8.2.2. Solicited local adverse events

All subjects in the immunogenicity sub-cohort 2:

The results are detailed in the following table:

Table 213 Percentage of subjects reporting each solicited local symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- Immunogenicity sub-cohort 2)

- During the 8-day (Day 0- Day 7) follow-up period, redness was the most frequently reported solicited local symptom for 13.3% subjects in the HRV group and 8.6% subjects in the placebo group. The most frequently reported grade "3" solicited local AEs were pain for 1.3% of subjects in the HRV group and redness for 0.7% of subjects in the placebo group. The solicited local symptoms were related to DTPa vaccine given intramuscularly (Table 213).

### 8.2.3. Solicited general adverse events

The results are detailed in the following tables:

Table 214 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort)

Table 215 Percentage of doses and subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

Table 216 Percentage of subjects reporting fever during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

Table 217 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

Table 218 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- except immunogenicity sub-cohort 2)

Table 219 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination

during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

Table 220 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- Immunogenicity sub-cohort 2)

All subjects except immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 27.4% subjects in the HRV group and 29.6% subjects in the placebo group Table 218).
- Irritability/fussiness was reported for 21.5% [95% CI: 19.4%; 23.6%] and 12.9% [95% CI: 11.2%; 14.7%] subjects after the first and second dose of HRV vaccine, respectively (Table 217).

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 36.6% subjects in the HRV group and 34.0% subjects in the placebo group. No more than 3.3% of the subjects in both groups reported irritability/fussiness rated as grade "3" in intensity (Table 220).
- Irritability/fussiness was reported for 28.8% [95% CI: 21.7%; 36.6%] and 18.7% [95% CI: 12.8%; 25.8%] subjects after the first and second dose of HRV vaccine, respectively (Table 219). Fever was reported for 3.9% subjects in the HRV group and 4.6% subjects in the placebo group (Table 220).

### 8.2.4. Unsolicited adverse events

The results are detailed in the following tables:

Table 221 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

Table 222 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

Table 223 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 18.6% in the HRV group and 22.1% in the placebo group (Table 221).
- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one grade “3” unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 0.1% in the HRV group and 0.2% in the placebo group (Table 223).
- The percentage of subjects reported for unsolicited AEs assessed as causally related to vaccination was 0.5% in the HRV group and 0.4% in the placebo group (Table 225).

## 8.3. According-to-protocol cohort analysis

The analysis of safety was based on the TVC. As the percentage of enrolled subjects excluded from the ATP cohort for safety was lower than 5% in both groups, no analysis based on the ATP cohort was performed.

## 8.4. Serious adverse events

During the study period, the percentage of subjects reported for at least one SAE was 11.0% (183/1666) in the HRV group and 14.8% (246/1667) in the placebo group. [redacted] None of the SAEs reported in the HRV group were causally related to the vaccine as assessed by the investigator. [redacted] The serious adverse event (SAE) Summary Table(s) are in Section 14.1 and the SAE CIOMS reports are in Section 14.2.

### 8.4.1. Fatal events

Of the 13 deaths (6 in the HRV group and 7 in the placebo group) reported during the study period, none were assessed as causally related to vaccination by the investigator (Table 240 and section 14.1).

### 8.4.2. Non-fatal events

A total of 659 SAEs (289 in the HRV group and 370 in the placebo group) were reported throughout the study (Section 14.1).

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

Eighteen subjects (8 in the HRV group and 10 in the placebo group) experienced unsolicited AEs or SAEs, leading to premature discontinuation from the study (Table 241).

Placebo group

- [redacted] This subject experienced the SAE four days post-Dose 1 of the placebo and it lasted for a period of 8 days. The subject was hospitalised and the outcome of the SAE was recovered/resolved. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the AE 22 days post-Dose 1 of the placebo and the end date was reported as “missing confirmed”. The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.

- [redacted] This subject experienced the AE 14 days post-Dose 1 of the placebo and the end date was reported as "missing confirmed". The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.
- [redacted] This subject experienced the SAE 356 days post-Dose 2 of the placebo, it lasted for a period of 30 days and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the AE three days post-Dose 1 of the placebo it lasted for a period of 39 days. The subject was treated and the outcome was recovered/resolved. The AE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE one day post-Dose 1 of the placebo it lasted for a period of 21 days. The subject was hospitalized and the outcome was recovered/resolved. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE 18 days post-Dose 2 of the placebo, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE 530 days post-Dose 2 of the placebo, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAE 36 days post-Dose 2 of the placebo, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.
- [redacted] This subject experienced the SAEs 107 days and 111 days post-Dose 2 of the placebo, respectively. The SAEs lasted for period of 5 days and one day, respectively, and the subject died. The SAE was assessed by the investigator as causally not related to vaccination.

HRV group

- [redacted] This subject experienced the SAE 496 days post-Dose 2 of the HRV vaccine and it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the AE nine days post-Dose 1 of the HRV vaccine and the end date was

reported as "missing confirmed". The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.

- [redacted] This subject experienced the AE seven days post-Dose 1 of the HRV vaccine and the end date was reported as "missing confirmed". The subject was treated and the outcome was recovered/resolved. The causality of the AE was reported as missing confirmed.
- [redacted] The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 2 days post-Dose 1 of the HRV vaccine and it lasted for two days and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 118 days post-Dose 2 of the HRV vaccine, it lasted for a period of 47 days and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 95 days post-Dose 2 of the HRV vaccine, it lasted for a day and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.
- [redacted] This subject experienced the SAE 218 days post-Dose 2 of the HRV vaccine, it lasted for four days and the subject died. The SAE was assessed by the investigator as causally not related to the vaccine.

## 8.6. Concomitant medications /vaccinations

The results are detailed in the following tables:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects who received any concomitant medication was 9.5% in the HRV group and 11.5% in the placebo group. Antipyretic and antibiotic medications were received by 1.2% and 2.7% subjects in the HRV group and 2% and 3.8% subjects in the placebo group, respectively (Table 244).
- During the study period, the percentage of subjects who received any concomitant medication was 34.6% in the HRV group and 38.6% in the placebo group. Antipyretic and antibiotic medications were received by 7.3% and 18.6% subjects in the HRV group and 8.6% and 22.5% subjects in the placebo group, respectively (Table 245).

## 8.7. Safety summary

*Any Symptom:*

All subjects except immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any AEs (solicited or unsolicited) was 44.2% [95% CI: 41.7%; 46.8%] subjects in the HRV group and 47.3% [95% CI: 44.8%; 49.8%] subjects in the placebo group. Any AEs (solicited or unsolicited) were reported for 32.8% [95% CI: 30.4%; 35.2%] and 26.6% [95% CI: 24.4%; 29.0%] subjects after the first and second dose of HRV vaccine respectively. Any AEs (solicited or unsolicited) assessed as causally related to vaccination were reported by 15.8% [95% CI: 14.0%; 17.7%] subjects in HRV group and 14.7% [95% CI: 12.9%; 16.5%] subjects in the placebo group. No more than 11.2% of the subjects in both groups reported any AEs (solicited or unsolicited) rated as grade “3” in intensity.

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day follow-up period (Day 0 to Day 7), the percentage of subjects reported for any general symptoms (solicited or unsolicited) was 52.9% [95% CI 44.7%; 61.1%] subjects in the HRV group and 50.3% [95% CI: 42.1%; 58.5%] subjects in the placebo group. Any general symptoms (solicited or unsolicited) were reported for 42.5% [95% CI: 34.5%; 50.7%] and 30.0% [95% CI: 22.8%; 38.0%] subjects after the first and second dose of HRV vaccine, respectively. No more than 16.0% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade “3” in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.
- During the 8-day follow-up period (Day 0 to Day 7), any general symptoms (solicited or unsolicited) rated as grade “3” in intensity and causally related to vaccination were reported for 2.6% [95% CI: 0.7%; 6.6%] subjects in the HRV group and 2.0% [95% CI: 0.4%; 5.6%] subjects in the placebo group. No more than 1.3% of the subjects in both groups reported any local symptoms (solicited or unsolicited) rated as grade “3” in intensity after the dose of DTPa co-administered with second dose of HRV/Placebo vaccine.

- During the 8-day follow-up period (Day 0 to Day 7), any AEs (solicited or unsolicited) requiring medical attention were reported for 12.4% [95% CI: 7.6%; 18.7%] subjects in the HRV group and 11.1% [95% CI: 6.6%; 17.2%] subjects in the placebo group.

*Solicited symptoms:*

All subjects except immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 27.4% subjects in the HRV group and 29.6% subjects in the placebo group. Irritability/fussiness was reported for 21.5% [95% CI: 19.4%; 23.6%] and 12.9% [95% CI: 11.2%; 14.7%] subjects after the first and second dose of HRV vaccine, respectively.

All subjects in the immunogenicity sub-cohort 2:

- During the 8-day (Day 0 to Day 7) follow-up period, irritability/fussiness was the most frequently reported solicited AE for 36.6% subjects in the HRV group and 34.0% subjects in the placebo group. Irritability/fussiness was reported for 28.8% [95% CI: 21.7%; 36.6%] and 18.7% [95% CI: 12.8%; 25.8%] subjects after the first and second dose of HRV vaccine, respectively. No more than 3.3% of the subjects in both groups reported irritability/fussiness rated as grade “3” in intensity.
- During the 8-day (Day 0- Day 7) follow-up period, redness was the most frequently reported solicited local symptom for 13.3% subjects in the HRV group and 8.6% subjects in the placebo group. The most frequently reported grade “3” solicited local AEs were pain for 1.3% of subjects in the HRV group and redness for 0.7% of subjects in the placebo group. The solicited local symptoms were related to DTPa vaccine given intramuscularly.

All subjects:

*Unsolicited symptoms:*

- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 18.6% in the HRV group and 22.1% in the placebo group.
- During the 31-day follow-up period (Day 0 to Day 30), the percentage of subjects reported for at least one grade “3” unsolicited AE classified by MedDRA System Organ Class and Preferred Term was 0.1% in the HRV group and 0.2% in the placebo group. The percentage of subjects reported for unsolicited AEs assessed as causally related to vaccination was 0.5% in the HRV group and 0.4% in the placebo group.

*Serious adverse events:*

- During the study period, the percentage of subjects reported for at least one SAE was 11.0% (183/1666) in the HRV group and 14.8% (246/1667) in the placebo group. [redacted] None of the SAEs reported in the HRV group were causally related to the vaccine as assessed by the investigator. [redacted]
- Of the 13 deaths (6 in the HRV group and 7 in the placebo group) reported during the study period, none of the fatal SAEs were assessed as causally related to vaccination by the investigator.

*Withdrawals due to adverse events /serious adverse events:*

- Eighteen subjects (8 in the HRV group and 10 in the placebo group) experienced unsolicited AEs or SAEs, leading to premature discontinuation from the study.

# 9. DISCUSSION

This phase III, double-blind study was conducted to evaluate the efficacy of two doses of the liquid HRV vaccine in the Chinese population from 2 weeks post-dose 2 up to approximately two years of age. The safety of the liquid HRV vaccine was also evaluated.

Two doses of the HRV vaccine were found to be efficacious against severe RV GE from 2 weeks after Dose 2 up to Visit 7 [72.0% (95% CI: 54.1%; 83.6%; p-value: <0.001)]. VE against severe RV GE from 2 weeks after Dose 2 up to Visit 6 was 75.0% [95% CI: 44.7%; 90.1%] and from after visit 6 up to Visit 7 was 70.2% [95% CI: 43.5%; 85.3%]. The observed vaccine efficacy ***over a period of two years,*** against severe RV GE in this study is in the range of the results of studies conducted in Latin America (***80.5%*** %) [95% CI: ***71.3*** %; ***87.1***%] [***Linhares***, ***2008***] and Africa (***59.0%; pooled two dose and three dose group***) [95% CI: ***1.0%***; ***83.0%***] [***Madhi, 2012***] but lower than what was observed in developed Asian countries (96.1%) [95% CI: 85.1%; 99.5%] [***Phua, 2009***] and EU (***90.4%***) [95% CI: ***85.1%***; ***94.1%***] [Vesikari, 2007]. Potential factors that may have contributed to the difference in estimates might include seasonality, time of enrolment in relation with the rotavirus season, the level of rotavirus exposure in the placebo group, differences in severity of RV GE episodes and potential differences in underlying host characteristics. **(Amended 14 August 2013)**

In this study, G1P[8] and G2P[4] were the most prevalent G1 and non-G1 RV strains identified from GE stool samples collected. Vaccine efficacy observed against any and severe RV GE caused by circulating wild type G1 RV from 2 weeks after Dose 2 up to Visit 7 was 52.2% [95% CI: 19.0%; 72.6%] and 64.0% [95% CI: 20.4%; 85.2%], respectively. Vaccine efficacy observed against any and severe GE caused by non-G1 RV from 2 weeks after Dose 2 up to Visit 7 was 62.1% [95% CI: 46.9%; 73.3%] and 77.8% [95% CI: 58.0%; 89.2%], respectively. A protection against RV GE caused by G2P[4] was demonstrated in this study.

The exploratory analysis performed using the Cox model showed that a total of 2.7 episodes of severe RV GE could be prevented per 100 infants vaccinated per year.

There were very few cases of hospitalised RV GE in the HRV vaccine group as compared to the placebo group (four subjects versus twenty one subjects) during the study period. Vaccine efficacy against hospitalisations due to severe RV GE was 81.0% [95% CI: 43.6%; 95.3%] and is comparable to the efficacy trial conducted in ***Latin America in*** the past: ***83.0% [95% CI: 73.1%; 89.7%] [Linhares, 2008].*** The burden associated with hospitalized RV GE in China is substantial as RV GE accounted for 32% - 50% of the hospitalised diarrhoea [Naghipour, 2008; Wang, 2009], and it could be reduced through the introduction of RV vaccines. **(Amended 14 August 2013)**

The safety profile was similar in both groups. The percentage of subjects with SAEs and AEs/SAEs leading to drop out was comparable in both groups. Two cases of intussusception (one in HRV group and one in placebo group) were reported during the study period and none of the cases were assessed as causally related to vaccination. From Dose 1 up to Visit 7, there were a total of 13 fatal events (6 subjects in the HRV group

and 7 subjects in the placebo group). Overall, the vaccine efficacy results obtained after 2 doses of liquid HRV vaccine are promising and indicate that including this vaccine in the public health programmes in countries with high incidence of RV GE would be of significant public health value.

# 10. OVERALL CONCLUSIONS (SUMMARY)

- Vaccine Efficacy against severe RV GE caused by the circulating wild-type RV during the efficacy follow up period (2 weeks post-Dose 2 up to Visit 7) was 72.0% (95% CI: 54.1%; 83.6%). The primary objective of this study was met.

# 11. TABLES AND FIGURES

## 11.1. Subject eligibility and attrition from the study

### 11.1.1. Number of subjects

**Table 14 Number of subjects by centre (Total vaccinated cohort)**

| | HRV | Placebo | Total | |
|---|---|---|---|---|
| Center | n | n | n | % |
| [redacted] | 600 | 600 | 1200 | 36.0 |
| | 452 | 452 | 904 | 27.1 |
| | 461 | 462 | 923 | 27.7 |
| | 153 | 153 | 306 | 9.2 |
| All | 1666 | 1667 | 3333 | 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

**Table 15 Subjects unblinded before database lock (13AUG2012) (Total vaccinated cohort)**

[redacted]

**Table 16 Number of subjects in the sub-cohorts (Total vaccinated cohort)**

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| Characteristics | Categories | n | % | n | % | n | % |
| Sub-cohort | Immunogenicity sub cohort 1 | 306 | 18.4 | 306 | 18.4 | 612 | 18.4 |
| | Immunogenicity sub cohort 2 | 153 | 9.2 | 153 | 9.2 | 306 | 9.2 |
| | All subjects except immunogenicity sub cohorts | 1207 | 72.4 | 1208 | 72.5 | 2415 | 72.5 |

N = number of subject number
n = number of subject number in a given category
% = n / Number of subject number with available results x 100
All subjects except immunogenicity sub cohorts - contains all the subjects for whom there is no blood sample planned in the study.

## 11.1.2. Study completion and withdrawal from study

### Table 17 Number of subjects entered, completed and withdrawn with reason for withdrawal till Visit 7 (Total vaccinated cohort)

| | HRV | Placebo | Total |
|---|---|---|---|
| **Number of subjects vaccinated** | 1666 | 1667 | 3333 |
| **Number of subjects completed** | 1518 | 1499 | 3017 |
| **Number of subjects withdrawn** | 148 | 168 | 316 |
| **Reasons for withdrawal :** | | | |
| Serious Adverse Event | 6 | 7 | 13 |
| Non-Serious Adverse Event | 4 | 8 | 12 |
| Protocol violation | 0 | 0 | 0 |
| Consent withdrawal (not due to an adverse event) | 55 | 46 | 101 |
| Migrated/moved from study area | 23 | 24 | 47 |
| Lost to follow-up (subjects with incomplete vaccination course) | 0 | 0 | 0 |
| Lost to follow-up (subjects with complete vaccination course) | 0 | 0 | 0 |
| Sponsor study termination | 0 | 0 | 0 |
| Other - diarrhea | 1 | 0 | 1 |
| Other - not willing to participate in the extended follow-up* (visit 7) | 59 | 83 | 142 |

Vaccinated= number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
*Second year follow up

### Table 18 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

| | Total | | | HRV | | Placebo | | NOGRP | |
|---|---|---|---|---|---|---|---|---|---|
| Title | n | s | % | n | s | n | s | n | s |
| Total cohort | 3340 | | | 1667 | | 1667 | | 6 | |
| Study vaccine dose not administrated but subject number allocated ( code 1030 ) | 7 | 7 | | 1 | 1 | 0 | 0 | 6 | 6 |
| Total vaccinated cohort | 3333 | | 100 | 1666 | | 1667 | | 0 | |
| Administration of vaccine(s) forbidden in the protocol ( code 1040 ) | 2 | 2 | | 1 | 1 | 1 | 1 | 0 | 0 |
| Randomisation code broken at the investigator site ( code 1060 ) | 2 | 2 | | 0 | 0 | 2 | 2 | 0 | 0 |
| Study vaccine dose not administered according to protocol ( code 1070 ) | 41 | 41 | | 22 | 22 | 19 | 19 | 0 | 0 |
| ATP cohort for safety | 3288 | | 98.6 | 1643 | | 1645 | | 0 | |
| At least one study vaccine dose not administered ( code 3010 ) | 133 | 137 | | 66 | 67 | 67 | 70 | 0 | 0 |
| Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response ( code 3030 ) | 7 | 8 | | 2 | 2 | 5 | 6 | 0 | 0 |
| ATP cohort for efficacy | 3148 | | 94.4 | 1575 | | 1573 | | 0 | |
| Subjects who do not have follow-up beyond visit 6 ( code 4020 ) | 169 | 307 | | 75 | 143 | 94 | 164 | 0 | 0 |
| ATP cohort for efficacy for second year follow-up | 2979 | | 89.4 | 1500 | | 1479 | | 0 | |

NOGRP = No assigned group
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

## 11.1.3. Protocol deviations

### Table 19 Protocol deviations not leading to exclusion of subjects or their data from analysis

| Protocol Deviation | Number of Subjects (%) |
|---|---|
| Non compliance to visit schedule | 71 |
| Vaccine administration in spite of storage temperature deviation outside recommended range | 34 |
| Inclusion/Exclusion criteria deviation | 31 |
| Administration of forbidden medication/Vaccine | 7 |
| Post-vaccination observation time less than 30 min | 7 |
| Stool sample shipment delayed by more than 3 days | 4 |
| Non-compliance to blood sampling schedule withdrawn refused for subject | 3 |
| Non investigational rotavirus vaccine administration | 2 |
| Blood withdrawn from subject belonging to non-immuno cohort | 2 |
| Delay in informing parents about the Subject Information Letter (Version 1 dated 13 October 2010) | 2 |
| Concomitant vaccination outside study centre | 2 |
| Delayed reporting of SAE | 1 |
| Body temperature not taken before vaccination | 1 |
| Concomitant vaccination outside visit window | 1 |
| Total | 168 |

# 11.2. Demographic characteristics

## 11.2.1. ATP cohort for efficacy

### Table 20 Summary of demographic characteristics (ATP cohort for efficacy)

| | | HRV N = 1575 | | Placebo N = 1573 | | Total N = 3148 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.5 | - | 9.7 | - | 9.6 | - |
| | SD | 2.63 | - | 2.56 | - | 2.60 | - |
| | Median | 9.0 | - | 9.0 | - | 9.0 | - |
| | Minimum | 5 | - | 5 | - | 5 | - |
| | Maximum | 16 | - | 16 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.1 | - | 14.2 | - | 14.1 | - |
| | SD | 2.78 | - | 2.64 | - | 2.71 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 9 | - | 10 | - | 9 | - |
| | Maximum | 26 | - | 22 | - | 26 | - |
| Age (months) at visit 6/last contact | Mean | 11.4 | - | 11.4 | - | 11.4 | - |
| | SD | 0.64 | - | 0.68 | - | 0.66 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 4 | - | 3 | - | 3 | - |
| | Maximum | 15 | - | 18 | - | 18 | - |
| Age (months) at visit 7 | Mean | 19.7 | - | 19.8 | - | 19.8 | - |
| | SD | 1.42 | - | 1.37 | - | 1.40 | - |
| | Median | 20.0 | - | 20.0 | - | 20.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 80 | - | 98 | - | 178 | - |
| Gender | Female | 758 | 48.1 | 793 | 50.4 | 1551 | 49.3 |
| | Male | 817 | 51.9 | 780 | 49.6 | 1597 | 50.7 |
| Geographic Ancestry | Asian-Chinese heritage | 1575 | 100 | 1573 | 100 | 3148 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

**Table 21 Summary of vital signs characteristics at Visit 1 (Day 0) (ATP cohort for efficacy)**

| | | HRV (N = 1575) | Placebo (N = 1573) | Total (N = 3148) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.8 | 59.0 | 58.9 |
| | SD | 2.92 | 2.91 | 2.92 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 49.0 | 46.0 | 46.0 |
| | Maximum | 70.0 | 72.0 | 72.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.6 | 5.7 | 5.7 |
| | SD | 0.84 | 0.85 | 0.84 |
| | Median | 5.6 | 5.7 | 5.6 |
| | Minimum | 3.0 | 3.0 | 3.0 |
| | Maximum | 9.5 | 9.0 | 9.5 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 16.3 | 16.3 | 16.3 |
| | SD | 1.84 | 1.88 | 1.86 |
| | Median | 16.1 | 16.3 | 16.1 |
| | Minimum | 11.7 | 8.9 | 8.9 |
| | Maximum | 25.5 | 26.8 | 26.8 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.26 | 1.25 | 1.25 |
| | Median | 39.3 | 39.4 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## 11.2.2. Total Vaccinated cohort

### Table 22 Summary of demographic characteristics (Total Vaccinated cohort)

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.5 | - | 9.7 | - | 9.6 | - |
| | SD | 2.64 | - | 2.59 | - | 2.62 | - |
| | Median | 9.0 | - | 9.0 | - | 9.0 | - |
| | Minimum | 5 | - | 5 | - | 5 | - |
| | Maximum | 16 | - | 16 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.1 | - | 14.2 | - | 14.1 | - |
| | SD | 2.79 | - | 2.64 | - | 2.72 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 9 | - | 10 | - | 9 | - |
| | Maximum | 26 | - | 22 | - | 26 | - |
| | Unknown | 67 | - | 70 | - | 137 | - |
| Age (months) at visit 6/last contact | Mean | 11.1 | - | 11.1 | - | 11.1 | - |
| | SD | 1.68 | - | 1.69 | - | 1.69 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 2 | - | 2 | - | 2 | - |
| | Maximum | 15 | - | 18 | - | 18 | - |
| Age (months) at visit 7 | Mean | 19.7 | - | 19.8 | - | 19.8 | - |
| | SD | 1.43 | - | 1.38 | - | 1.40 | - |
| | Median | 20.0 | - | 20.0 | - | 20.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 148 | - | 168 | - | 316 | - |
| Gender | Female | 795 | 47.7 | 836 | 50.1 | 1631 | 48.9 |
| | Male | 871 | 52.3 | 831 | 49.9 | 1702 | 51.1 |
| Geographic Ancestry | Asian-Chinese heritage | 1666 | 100 | 1667 | 100 | 3333 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 23 Summary of demographic characteristics (Total vaccinated cohort-Immunogenicity sub cohort 1)

| | | HRV N = 306 | | Placebo N = 306 | | Total N = 612 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 10.2 | - | 10.1 | - | 10.2 | - |
| | SD | 2.97 | - | 2.81 | - | 2.89 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 5 | - | 6 | - | 5 | - |
| | Maximum | 16 | - | 15 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.7 | - | 14.6 | - | 14.6 | - |
| | SD | 3.10 | - | 2.93 | - | 3.01 | - |
| | Median | 14.0 | - | 14.0 | - | 14.0 | - |
| | Minimum | 10 | - | 10 | - | 10 | - |
| | Maximum | 23 | - | 22 | - | 23 | - |
| | Unknown | 18 | - | 19 | - | 37 | - |
| Age (months) at visit 6/last contact | Mean | 10.9 | - | 10.9 | - | 10.9 | - |
| | SD | 1.97 | - | 1.99 | - | 1.98 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 2 | - | 2 | - | 2 | - |
| | Maximum | 14 | - | 13 | - | 14 | - |
| Age (months) at visit 7 | Mean | 21.0 | - | 20.9 | - | 21.0 | - |
| | SD | 1.00 | - | 0.93 | - | 0.97 | - |
| | Median | 21.0 | - | 21.0 | - | 21.0 | - |
| | Minimum | 19 | - | 19 | - | 19 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 34 | - | 39 | - | 73 | - |
| Gender | Female | 153 | 50.0 | 153 | 50.0 | 306 | 50.0 |
| | Male | 153 | 50.0 | 153 | 50.0 | 306 | 50.0 |
| Geographic Ancestry | Asian-Chinese heritage | 306 | 100 | 306 | 100 | 612 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 24 Summary of demographic characteristics (Total vaccinated cohort-Immunogenicity sub cohort 2)

| | | HRV N = 153 | | Placebo N = 153 | | Total N = 306 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.8 | - | 10.1 | - | 10.0 | - |
| | SD | 1.30 | - | 1.29 | - | 1.30 | - |
| | Median | 10.0 | - | 10.0 | - | 10.0 | - |
| | Minimum | 8 | - | 8 | - | 8 | - |
| | Maximum | 12 | - | 12 | - | 12 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 14.3 | - | 14.6 | - | 14.5 | - |
| | SD | 1.27 | - | 1.32 | - | 1.30 | - |
| | Median | 14.0 | - | 15.0 | - | 14.0 | - |
| | Minimum | 12 | - | 12 | - | 12 | - |
| | Maximum | 17 | - | 17 | - | 17 | - |
| | Unknown | 3 | - | 2 | - | 5 | - |
| Age (months) at visit 6/last contact | Mean | 11.2 | - | 11.2 | - | 11.2 | - |
| | SD | 1.19 | - | 1.30 | - | 1.24 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 5 | - | 3 | - | 3 | - |
| | Maximum | 14 | - | 13 | - | 14 | - |
| Age (months) at visit 7 | Mean | 18.9 | - | 19.0 | - | 19.0 | - |
| | SD | 1.12 | - | 1.14 | - | 1.13 | - |
| | Median | 19.0 | - | 19.0 | - | 19.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 21 | - | 21 | - | 21 | - |
| | Unknown | 15 | - | 12 | - | 27 | - |
| Gender | Female | 72 | 47.1 | 82 | 53.6 | 154 | 50.3 |
| | Male | 81 | 52.9 | 71 | 46.4 | 152 | 49.7 |
| Geographic Ancestry | Asian-Chinese heritage | 153 | 100 | 153 | 100 | 306 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 25 Summary of demographic characteristics (Total vaccinated cohort-except Immunogenicity sub cohorts)

| | | HRV N = 1207 | | Placebo N = 1208 | | Total N = 2415 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** | **Value or n** | **%** |
| Age (weeks) at vaccination dose 1 of HRV/placebo | Mean | 9.3 | - | 9.6 | - | 9.4 | - |
| | SD | 2.65 | - | 2.64 | - | 2.65 | - |
| | Median | 9.0 | - | 9.0 | - | 9.0 | - |
| | Minimum | 6 | - | 5 | - | 5 | - |
| | Maximum | 16 | - | 16 | - | 16 | - |
| Age (weeks) at vaccination dose 2 of HRV/placebo | Mean | 13.9 | - | 14.0 | - | 14.0 | - |
| | SD | 2.83 | - | 2.68 | - | 2.76 | - |
| | Median | 13.0 | - | 14.0 | - | 13.0 | - |
| | Minimum | 9 | - | 10 | - | 9 | - |
| | Maximum | 26 | - | 21 | - | 26 | - |
| | Unknown | 46 | - | 49 | - | 95 | - |
| Age (months) at visit 6/last contact | Mean | 11.2 | - | 11.1 | - | 11.2 | - |
| | SD | 1.65 | - | 1.65 | - | 1.65 | - |
| | Median | 11.0 | - | 11.0 | - | 11.0 | - |
| | Minimum | 2 | - | 2 | - | 2 | - |
| | Maximum | 15 | - | 18 | - | 18 | - |
| Age (months) at visit 7 | Mean | 19.5 | - | 19.6 | - | 19.6 | - |
| | SD | 1.38 | - | 1.33 | - | 1.36 | - |
| | Median | 19.0 | - | 19.0 | - | 19.0 | - |
| | Minimum | 17 | - | 17 | - | 17 | - |
| | Maximum | 23 | - | 23 | - | 23 | - |
| | Unknown | 99 | - | 117 | - | 216 | - |
| Gender | Female | 570 | 47.2 | 601 | 49.8 | 1171 | 48.5 |
| | Male | 637 | 52.8 | 607 | 50.2 | 1244 | 51.5 |
| Geographic Ancestry | Asian-Chinese heritage | 1207 | 100 | 1208 | 100 | 2415 | 100 |
| | Other | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 26 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort)

| | | HRV (N = 1666) | Placebo (N = 1667) | Total (N = 3333) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.8 | 59.0 | 58.9 |
| | SD | 2.93 | 2.93 | 2.93 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 49.0 | 46.0 | 46.0 |
| | Maximum | 70.0 | 72.0 | 72.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.7 | 5.7 | 5.7 |
| | SD | 0.85 | 0.85 | 0.85 |
| | Median | 5.6 | 5.7 | 5.6 |
| | Minimum | 3.0 | 3.0 | 3.0 |
| | Maximum | 9.5 | 9.0 | 9.5 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 16.3 | 16.4 | 16.3 |
| | SD | 1.84 | 1.87 | 1.85 |
| | Median | 16.1 | 16.3 | 16.2 |
| | Minimum | 11.7 | 8.9 | 8.9 |
| | Maximum | 25.5 | 26.8 | 26.8 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.25 | 1.26 | 1.25 |
| | Median | 39.3 | 39.3 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## Table 27 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort- Immunogenicity sub cohort 1)

| | | HRV (N = 306) | Placebo (N = 306) | Total (N = 612) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 59.2 | 59.3 | 59.3 |
| | SD | 2.84 | 2.91 | 2.87 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 52.0 | 46.0 | 46.0 |
| | Maximum | 68.0 | 67.0 | 68.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.6 | 5.6 | 5.6 |
| | SD | 0.85 | 0.83 | 0.84 |
| | Median | 5.4 | 5.7 | 5.5 |
| | Minimum | 3.7 | 3.4 | 3.4 |
| | Maximum | 8.3 | 7.9 | 8.3 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 15.8 | 16.0 | 15.9 |
| | SD | 1.59 | 1.74 | 1.67 |
| | Median | 15.6 | 15.9 | 15.8 |
| | Minimum | 11.7 | 11.1 | 11.1 |
| | Maximum | 20.8 | 22.2 | 22.2 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.36 | 1.29 | 1.33 |
| | Median | 39.3 | 39.3 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

**Table 28 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort- Immunogenicity sub cohort 2)**

| | | HRV (N = 153) | Placebo (N = 153) | Total (N = 306) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.8 | 59.4 | 59.1 |
| | SD | 2.86 | 2.62 | 2.76 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 50.0 | 53.0 | 50.0 |
| | Maximum | 67.0 | 67.0 | 67.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 6.0 | 6.0 | 6.0 |
| | SD | 0.83 | 0.78 | 0.81 |
| | Median | 6.0 | 6.0 | 6.0 |
| | Minimum | 3.0 | 3.8 | 3.0 |
| | Maximum | 9.5 | 8.0 | 9.5 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 17.4 | 17.0 | 17.2 |
| | SD | 1.90 | 1.93 | 1.92 |
| | Median | 17.2 | 16.9 | 16.9 |
| | Minimum | 12.0 | 11.3 | 11.3 |
| | Maximum | 25.5 | 23.9 | 25.5 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.5 | 39.4 |
| | SD | 1.11 | 1.22 | 1.17 |
| | Median | 39.3 | 39.4 | 39.4 |
| | Minimum | 36.6 | 36.3 | 36.3 |
| | Maximum | 42.0 | 42.4 | 42.4 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## Table 29 Summary of vital signs characteristics at Visit 1 (Day 0) (Total vaccinated cohort- except immunogenicity sub cohorts)

| | | HRV (N = 1207) | Placebo (N = 1208) | Total (N = 2415) |
|---|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** | **Value** |
| Height (cm) at visit 1 | Mean | 58.7 | 58.9 | 58.8 |
| | SD | 2.95 | 2.96 | 2.95 |
| | Median | 59.0 | 59.0 | 59.0 |
| | Minimum | 49.0 | 51.0 | 49.0 |
| | Maximum | 70.0 | 72.0 | 72.0 |
| | Unknown | 0 | 0 | 0 |
| Weight (kg) at visit 1 | Mean | 5.6 | 5.7 | 5.7 |
| | SD | 0.84 | 0.86 | 0.85 |
| | Median | 5.6 | 5.6 | 5.6 |
| | Minimum | 3.1 | 3.0 | 3.0 |
| | Maximum | 9.4 | 9.0 | 9.4 |
| | Unknown | 0 | 0 | 0 |
| BMI (kg/m²) | Mean | 16.3 | 16.4 | 16.3 |
| | SD | 1.83 | 1.88 | 1.85 |
| | Median | 16.1 | 16.4 | 16.3 |
| | Minimum | 11.9 | 8.9 | 8.9 |
| | Maximum | 24.6 | 26.8 | 26.8 |
| | Unknown | 0 | 0 | 0 |
| Gestational Age (weeks) | Mean | 39.3 | 39.3 | 39.3 |
| | SD | 1.24 | 1.25 | 1.25 |
| | Median | 39.3 | 39.3 | 39.3 |
| | Minimum | 36.0 | 36.0 | 36.0 |
| | Maximum | 42.6 | 42.6 | 42.6 |
| | Unknown | 0 | 0 | 0 |

N = total number of subjects
Value = value of the considered parameter
SD = standard deviation
Age (weeks)= age expressed in weeks
Height (cm) = height expressed in centimeters
Weight (kg) = weight expressed in Kilograms

## 11.3. Concomitant and Intercurrent Vaccinations

### Table 30 Summary of co-administered vaccination by dose (Total vaccinated cohort- except immunogenicity sub cohort 2)

| | HRV N = 1513 | | Placebo N = 1514 | | Total N = 3027 | |
|---|---|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Dose 1** | | | | | | |
| Any | 4 | 0.3 | 5 | 0.3 | 9 | 0.3 |
| DPT | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| HBV | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| OPV | 2 | 0.1 | 5 | 0.3 | 7 | 0.2 |
| **Dose 2** | | | | | | |
| | **HRV N = 1449** | | **Placebo N = 1446** | | **Total N = 2895** | |
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any | 4 | 0.3 | 5 | 0.3 | 9 | 0.3 |
| DPT | 2 | 0.1 | 3 | 0.2 | 5 | 0.2 |
| HBV | 0 | 0.0 | 1 | 0.1 | 1 | 0.0 |
| OPV | 3 | 0.2 | 4 | 0.3 | 7 | 0.2 |

N= total number of subjects having received the considered dose of HRV/placebo
n/%= number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

**Table 31 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort- except immunogenicity sub cohort 2)**

| Before Dose 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV N = 1513 | | | Placebo N = 1514 | | | Total N = 3027 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 5179 | 1510 | 99.8 | 5220 | 1514 | 100 | 10399 | 3024 | 99.9 |
| BCG | 1508 | 1508 | 99.7 | 1510 | 1510 | 99.7 | 3018 | 3018 | 99.7 |
| DPT | 89 | 89 | 5.9 | 79 | 79 | 5.2 | 168 | 168 | 5.6 |
| DTPa | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 2944 | 1509 | 99.7 | 2964 | 1514 | 100 | 5908 | 3023 | 99.9 |
| HIB | 1 | 1 | 0.1 | 1 | 1 | 0.1 | 2 | 2 | 0.1 |
| OPV | 637 | 552 | 36.5 | 665 | 588 | 38.8 | 1302 | 1140 | 37.7 |
| **Between dose 1 and dose 2$** | | | | | | | | | |
| | HRV N = 1513 | | | Placebo N = 1514 | | | Total N = 3027 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 1713 | 1198 | 79.2 | 1776 | 1221 | 80.6 | 3489 | 2419 | 79.9 |
| BCG | 3 | 3 | 0.2 | 2 | 2 | 0.1 | 5 | 5 | 0.2 |
| DPT | 458 | 447 | 29.5 | 499 | 491 | 32.4 | 957 | 938 | 31.0 |
| HBV | 56 | 56 | 3.7 | 52 | 52 | 3.4 | 108 | 108 | 3.6 |
| HIB | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| OPV | 1195 | 1170 | 77.3 | 1223 | 1197 | 79.1 | 2418 | 2367 | 78.2 |
| **Between dose 2 and visit 3*** | | | | | | | | | |
| | HRV N = 1449 | | | Placebo N = 1446 | | | Total N = 2895 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 2670 | 1339 | 92.4 | 2676 | 1329 | 91.9 | 5346 | 2668 | 92.2 |
| DPT | 1304 | 1260 | 87.0 | 1333 | 1292 | 89.3 | 2637 | 2552 | 88.2 |
| FLU | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 20 | 20 | 1.4 | 9 | 9 | 0.6 | 29 | 29 | 1.0 |
| HIB | 0 | 0 | 0.0 | 4 | 3 | 0.2 | 4 | 3 | 0.1 |
| JE | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| MMR | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| MPSV | 6 | 5 | 0.3 | 2 | 2 | 0.1 | 8 | 7 | 0.2 |
| MR | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| OPV | 1337 | 1281 | 88.4 | 1323 | 1273 | 88.0 | 2660 | 2554 | 88.2 |

N= Before Dose 1 and between Dose 1 and Dose 2: total number of subjects having received dose 1 of HRV
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV 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 doses
$= upto last contact conclusion at Visit 3 if dose 2 of HRV was not administered
*= upto last contact conclusion at Visit 3 if visit 3 was not done

## Table 32 Summary of co-administered vaccination by dose (Total vaccinated cohort- Immunogenicity sub cohort 2)

| Dose 1 | | | | | | |
|---|---|---|---|---|---|---|
| | HRV N = 153 | | Placebo N = 153 | | Total N = 306 | |
| Characteristics | n | % | n | % | n | % |
| Any | 2 | 1.3 | 3 | 2.0 | 5 | 1.6 |
| BCG | 1 | 0.7 | 0 | 0.0 | 1 | 0.3 |
| HBV | 1 | 0.7 | 3 | 2.0 | 4 | 1.3 |
| **Dose 2** | | | | | | |
| | HRV N = 150 | | Placebo N = 151 | | Total N = 301 | |
| Characteristics | n | % | n | % | n | % |
| Any | 1 | 0.7 | 0 | 0.0 | 1 | 0.3 |
| HBV | 1 | 0.7 | 0 | 0.0 | 1 | 0.3 |

N= total number of subjects having received the considered dose of HRV/placebo
n/%= number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

## Table 33 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort- Immunogenicity sub cohort 2)

| Before Dose 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV N = 153 | | | Placebo N = 153 | | | Total N = 306 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 449 | 153 | 100 | 447 | 152 | 99.3 | 896 | 305 | 99.7 |
| BCG | 150 | 150 | 98.0 | 152 | 152 | 99.3 | 302 | 302 | 98.7 |
| HBV | 299 | 153 | 100 | 295 | 152 | 99.3 | 594 | 305 | 99.7 |
| **Between dose 1 and dose 2$** | | | | | | | | | |
| | HRV N = 153 | | | Placebo N = 153 | | | Total N = 306 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 4 | 3 | 2.0 | 8 | 7 | 4.6 | 12 | 10 | 3.3 |
| BCG | 1 | 1 | 0.7 | 1 | 1 | 0.7 | 2 | 2 | 0.7 |
| DPT | 0 | 0 | 0.0 | 1 | 1 | 0.7 | 1 | 1 | 0.3 |
| HBV | 3 | 3 | 2.0 | 6 | 6 | 3.9 | 9 | 9 | 2.9 |
| **Between dose 2 and visit 3*** | | | | | | | | | |
| | HRV N = 150 | | | Placebo N = 151 | | | Total N = 301 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 1 | 1 | 0.7 | 1 | 1 | 0.7 | 2 | 2 | 0.7 |
| HBV | 1 | 1 | 0.7 | 1 | 1 | 0.7 | 2 | 2 | 0.7 |

N= Before Dose 1 and between Dose 1 and Dose 2: total number of subjects having received dose 1 of HRV
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV 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 doses
% = n / Number of subject number with available results x 100
$= upto last contact conclusion at Visit 3 if dose 2 of HRV was not administered
*= upto last contact conclusion at Visit 3 if visit 3 was not done

## Table 34 Summary of co-administered vaccination by dose (Total vaccinated cohort)

| Dose 1 | | | | | | |
|---|---|---|---|---|---|---|
| | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any | 6 | 0.4 | 8 | 0.5 | 14 | 0.4 |
| BCG | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| DPT | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| HBV | 3 | 0.2 | 3 | 0.2 | 6 | 0.2 |
| OPV | 2 | 0.1 | 5 | 0.3 | 7 | 0.2 |
| **Dose 2** | | | | | | |
| | HRV N = 1599 | | Placebo N = 1597 | | Total N = 3196 | |
| **Characteristics** | **n** | **%** | **n** | **%** | **n** | **%** |
| Any | 5 | 0.3 | 5 | 0.3 | 10 | 0.3 |
| DPT | 2 | 0.1 | 3 | 0.2 | 5 | 0.2 |
| HBV | 1 | 0.1 | 1 | 0.1 | 2 | 0.1 |
| OPV | 3 | 0.2 | 4 | 0.3 | 7 | 0.2 |

N= total number of subjects having received the considered dose of HRV/placebo
n/%= number/percentage of subjects who received the specified vaccination on the same day as the considered dose of HRV/placebo

## Table 35 Summary of vaccinations other than HRV/placebo administered during the study period, excluding vaccination given on the day of HRV/placebo doses (Total vaccinated cohort)

| Before Dose 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | HRV N = 1666 | | | Placebo N = 1667 | | | Total N = 3333 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 5628 | 1663 | 99.8 | 5667 | 1666 | 99.9 | 11295 | 3329 | 99.9 |
| BCG | 1658 | 1658 | 99.5 | 1662 | 1662 | 99.7 | 3320 | 3320 | 99.6 |
| DPT | 89 | 89 | 5.3 | 79 | 79 | 4.7 | 168 | 168 | 5.0 |
| DTPa | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 3243 | 1662 | 99.8 | 3259 | 1666 | 99.9 | 6502 | 3328 | 99.8 |
| HIB | 1 | 1 | 0.1 | 1 | 1 | 0.1 | 2 | 2 | 0.1 |
| OPV | 637 | 552 | 33.1 | 665 | 588 | 35.3 | 1302 | 1140 | 34.2 |
| **Between dose 1 and dose 2[$]** | | | | | | | | | |
| | HRV N = 1666 | | | Placebo N = 1667 | | | Total N = 3333 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 1717 | 1201 | 72.1 | 1784 | 1228 | 73.7 | 3501 | 2429 | 72.9 |
| BCG | 4 | 4 | 0.2 | 3 | 3 | 0.2 | 7 | 7 | 0.2 |
| DPT | 458 | 447 | 26.8 | 500 | 492 | 29.5 | 958 | 939 | 28.2 |
| HBV | 59 | 59 | 3.5 | 58 | 58 | 3.5 | 117 | 117 | 3.5 |
| HIB | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| OPV | 1195 | 1170 | 70.2 | 1223 | 1197 | 71.7 | 2418 | 2367 | 71.0 |
| **Between dose 2 and visit 3*** | | | | | | | | | |
| | HRV N = 1599 | | | Placebo N = 1597 | | | Total N = 3196 | | |
| Characteristics | # | n | % | # | n | % | # | n | % |
| Any | 2671 | 1340 | 83.8 | 2677 | 1330 | 83.3 | 5348 | 2670 | 83.5 |
| DPT | 1304 | 1260 | 78.8 | 1333 | 1292 | 80.9 | 2637 | 2552 | 79.8 |
| FLU | 0 | 0 | 0.0 | 1 | 1 | 0.1 | 1 | 1 | 0.0 |
| HBV | 21 | 21 | 1.3 | 10 | 10 | 0.6 | 31 | 31 | 1.0 |
| HIB | 0 | 0 | 0.0 | 4 | 3 | 0.2 | 4 | 3 | 0.1 |
| JE | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| MMR | 1 | 1 | 0.1 | 0 | 0 | 0.0 | 1 | 1 | 0.0 |
| MPSV | 6 | 5 | 0.3 | 2 | 2 | 0.1 | 8 | 7 | 0.2 |
| MR | 1 | 1 | 0.1 | 2 | 2 | 0.1 | 3 | 3 | 0.1 |
| OPV | 1337 | 1281 | 80.1 | 1323 | 1273 | 79.7 | 2660 | 2554 | 79.9 |

N= Before Dose 1 and between Dose 1 and Dose 2: total number of subjects having received dose 1 of HRV/placebo
Between Dose 2 and Visit 3: total number of subjects having received dose 2 of HRV/placebo
#= number of doses administered of the specified vaccination excluding vaccination given on the day of HRV/placebo doses
n/%= number/percentage of subjects who received at least one specified vaccination between the considered visits excluding vaccination given on the day of HRV/placebo doses
% = n / Number of subject number with available results x 100
$= upto last contact conclusion at Visit 3 if dose 2 of HRV/placebo was not administered
*= upto last contact conclusion at Visit 3 if visit 3 was not done

## 11.4. Efficacy results

### Table 36 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | | HRV N = 1575 | | Placebo N = 1573 | | Total N = 3148 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 847 | 53.8 | 814 | 51.7 | 1661 | 52.8 |
| | 1 | 461 | 29.3 | 462 | 29.4 | 923 | 29.3 |
| | 2 | 165 | 10.5 | 197 | 12.5 | 362 | 11.5 |
| | 3 | 68 | 4.3 | 53 | 3.4 | 121 | 3.8 |
| | 4 | 17 | 1.1 | 29 | 1.8 | 46 | 1.5 |
| | 5 | 7 | 0.4 | 10 | 0.6 | 17 | 0.5 |
| | 6 | 6 | 0.4 | 4 | 0.3 | 10 | 0.3 |
| | 7 | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| | 9 | 3 | 0.2 | 1 | 0.1 | 4 | 0.1 |
| | 10 | 0 | 0.0 | 1 | 0.1 | 1 | 0.0 |
| | Any | 728 | 46.2 | 759 | 48.3 | 1487 | 47.2 |
| RVGE | 0 | 1505 | 95.6 | 1406 | 89.4 | 2911 | 92.5 |
| | 1 | 70 | 4.4 | 164 | 10.4 | 234 | 7.4 |
| | 2 | 0 | 0.0 | 3 | 0.2 | 3 | 0.1 |
| | Any | 70 | 4.4 | 167 | 10.6 | 237 | 7.5 |
| Severe GE | 0 | 1388 | 88.1 | 1367 | 86.9 | 2755 | 87.5 |
| | 1 | 172 | 10.9 | 174 | 11.1 | 346 | 11.0 |
| | 2 | 8 | 0.5 | 27 | 1.7 | 35 | 1.1 |
| | 3 | 4 | 0.3 | 5 | 0.3 | 9 | 0.3 |
| | 4 | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| | 5 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 187 | 11.9 | 206 | 13.1 | 393 | 12.5 |
| Severe RVGE | 0 | 1554 | 98.7 | 1498 | 95.2 | 3052 | 97.0 |
| | 1 | 21 | 1.3 | 75 | 4.8 | 96 | 3.0 |
| | Any | 21 | 1.3 | 75 | 4.8 | 96 | 3.0 |

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

## Table 37 Number of GE episodes reported from 2 weeks after Dose 2 up to Visit 7 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 614 | 52.6 | 654 | 52.8 |
| | Moderate (7-10) | 341 | 29.2 | 340 | 27.5 |
| | Severe (≥11) | 213 | 18.2 | 243 | 19.6 |
| | Unknown | 0 | 0.0 | 1 | 0.1 |
| | Any | 1168 | 100 | 1237 | 99.9 |
| RVGE | Mild (1-6) | 28 | 40.0 | 45 | 26.5 |
| | Moderate (7-10) | 21 | 30.0 | 50 | 29.4 |
| | Severe (≥11) | 21 | 30.0 | 75 | 44.1 |
| | Any | 70 | 100 | 170 | 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

## Table 38 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| | HRV N' = 1168 | | Placebo N' = 1238 | | Total N' = 2406 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 56 | 4.8 | 67 | 5.4 | 123 | 5.1 |
| no stools collected* | 54 | 4.6 | 66 | 5.3 | 120 | 5.0 |
| stools collected but no results available | 2 | 0.2 | 1 | 0.1 | 3 | 0.1 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category
*There is one episode of GE for which sample was collected but was not sent to lab. Hence the sample was not tested.

## Table 39 Percentage of subjects with RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

| | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| Serotype | n | % | n | % |
| Any | 70 | 4.4 | 167 | 10.6 |
| G1 WT | 22 | 1.4 | 46 | 2.9 |
| G2 | 42 | 2.7 | 105 | 6.7 |
| G3 | 1 | 0.1 | 12 | 0.8 |
| G9 | 1 | 0.1 | 5 | 0.3 |
| GX | 6 | 0.4 | 8 | 0.5 |
| P4 | 43 | 2.7 | 107 | 6.8 |
| P8 WT | 25 | 1.6 | 59 | 3.8 |
| P9 | 0 | 0.0 | 1 | 0.1 |
| PX | 4 | 0.3 | 1 | 0.1 |

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=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 40 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 2 up to Visit 7 by G type and P type (ATP cohort for efficacy)

| | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 21 | 1.3 | 75 | 4.8 |
| G1 WT | 9 | 0.6 | 25 | 1.6 |
| G2 | 11 | 0.7 | 43 | 2.7 |
| G3 | 0 | 0.0 | 3 | 0.2 |
| G9 | 0 | 0.0 | 3 | 0.2 |
| GX | 1 | 0.1 | 6 | 0.4 |
| P4 | 12 | 0.8 | 43 | 2.7 |
| P8 WT | 9 | 0.6 | 31 | 2.0 |
| PX | 1 | 0.1 | 1 | 0.1 |

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 severe RV GE episode whatever the serotype
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 41 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=70 | | Placebo N'=170 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+G2+P4 | 0 | 0.00 | 4 | 2.35 |
| G1WT+G2+P4+P8WT | 1 | 1.43 | 1 | 0.59 |
| G1WT+G2+P8WT | 0 | 0.00 | 3 | 1.76 |
| G1WT+P4 | 1 | 1.43 | 5 | 2.94 |
| G1WT+P8WT | 19 | 27.14 | 34 | 20.00 |
| G1WT+PX | 1 | 1.43 | 0 | 0.00 |
| G2+G3+P4 | 1 | 1.43 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 0.59 |
| G2+P4 | 39 | 55.71 | 97 | 57.06 |
| G2+P4+P8WT | 1 | 1.43 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 0.59 |
| G3+P8WT | 0 | 0.00 | 10 | 5.88 |
| G3+P9 | 0 | 0.00 | 1 | 0.59 |
| G9+P8WT | 1 | 1.43 | 5 | 2.94 |
| GX | 0 | 0.00 | 2 | 1.18 |
| GX+P8WT | 3 | 4.29 | 6 | 3.53 |
| GX+PX | 3 | 4.29 | 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 2 of HRV vaccine or placebo up to visit 7
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 42 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=21 | | Placebo N'=75 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 2 | 2.67 |
| G1WT+G2+P8WT | 0 | 0.00 | 2 | 2.67 |
| G1WT+P4 | 1 | 4.76 | 3 | 4.00 |
| G1WT+P8WT | 8 | 38.10 | 18 | 24.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.33 |
| G2+P4 | 10 | 47.62 | 37 | 49.33 |
| G2+P4+P8WT | 1 | 4.76 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.33 |
| G3+P8WT | 0 | 0.00 | 2 | 2.67 |
| G9+P8WT | 0 | 0.00 | 3 | 4.00 |
| GX | 0 | 0.00 | 1 | 1.33 |
| GX+P8WT | 0 | 0.00 | 5 | 6.67 |
| GX+PX | 1 | 4.76 | 0 | 0.00 |

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 severe RV GE episodes reported from 2 weeks after dose 2 of HRV vaccine or placebo up to visit 7
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 43 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | HRV N' = 70 | | Placebo N' = 170 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.0 | - | 10.0 | - |
| | SD | 3.8 | - | 4.6 | - |
| | Median | 8.0 | - | 10.0 | - |
| | Minimum | 2.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 60 | 85.7 | 101 | 59.4 |
| | 5 | 7 | 10.0 | 28 | 16.5 |
| | more than 5 days | 3 | 4.3 | 41 | 24.1 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 7 | 10.0 | 19 | 11.2 |
| | 4 to 5 | 36 | 51.4 | 75 | 44.1 |
| | more than 5 | 27 | 38.6 | 76 | 44.7 |
| Duration of vomiting (days) | 0 day | 39 | 55.7 | 62 | 36.5 |
| | 1 day | 11 | 15.7 | 46 | 27.1 |
| | 2 days | 16 | 22.9 | 30 | 17.6 |
| | more than 2 days | 4 | 5.7 | 32 | 18.8 |
| Max number of episodes of vomiting /day | 0 | 39 | 55.7 | 62 | 36.5 |
| | 1 | 7 | 10.0 | 28 | 16.5 |
| | 2 to 4 | 22 | 31.4 | 62 | 36.5 |
| | more than 4 | 2 | 2.9 | 18 | 10.6 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 15 | 21.4 | 41 | 24.1 |
| | | | | | |
| | 36.6 to 37.9°C | 34 | 48.6 | 72 | 42.4 |
| | 38.0 to 38.4°C | 13 | 18.6 | 18 | 10.6 |
| | more than 38.4°C | 8 | 11.4 | 39 | 22.9 |
| Treatment | none | 37 | 52.9 | 72 | 42.4 |
| | rehydration | 29 | 41.4 | 77 | 45.3 |
| | hospitalization | 4 | 5.7 | 21 | 12.4 |
| Dehydration | none | 37 | 52.9 | 72 | 42.4 |
| | 1 to 5% | 13 | 18.6 | 18 | 10.6 |
| | more than 5 % | 20 | 28.6 | 80 | 47.1 |

N' = number of RV GE episodes reported in each group
n/% = number/percentage of specified symptom reported in each group among N'
Value= value of the considered parameter
SD= standard deviation
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5>5% dehydration)

**Table 44 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G1WT type (ATP cohort for efficacy)**

| | | HRV N' = 22 | | Placebo N' = 47 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.8 | - | 11.2 | - |
| | SD | 4.0 | - | 4.4 | - |
| | Median | 9.5 | - | 11.0 | - |
| | Minimum | 2.0 | - | 3.0 | - |
| | Maximum | 16.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 21 | 95.5 | 24 | 51.1 |
| | 5 | 1 | 4.5 | 10 | 21.3 |
| | more than 5 days | 0 | 0.0 | 13 | 27.7 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 2 | 9.1 | 1 | 2.1 |
| | 4 to 5 | 9 | 40.9 | 28 | 59.6 |
| | more than 5 | 11 | 50.0 | 18 | 38.3 |
| Duration of vomiting (days) | 0 day | 12 | 54.5 | 12 | 25.5 |
| | 1 day | 2 | 9.1 | 15 | 31.9 |
| | 2 days | 6 | 27.3 | 11 | 23.4 |
| | more than 2 days | 2 | 9.1 | 9 | 19.1 |
| Max number of episodes of vomiting /day | 0 | 12 | 54.5 | 12 | 25.5 |
| | 1 | 2 | 9.1 | 9 | 19.1 |
| | 2 to 4 | 7 | 31.8 | 19 | 40.4 |
| | more than 4 | 1 | 4.5 | 7 | 14.9 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 3 | 13.6 | 9 | 19.1 |
| | 36.6 to 37.9°C | 8 | 36.4 | 20 | 42.6 |
| | 38.0 to 38.4°C | 7 | 31.8 | 6 | 12.8 |
| | more than 38.4°C | 4 | 18.2 | 12 | 25.5 |
| Treatment | none | 10 | 45.5 | 15 | 31.9 |
| | rehydration | 11 | 50.0 | 24 | 51.1 |
| | hospitalization | 1 | 4.5 | 8 | 17.0 |
| Dehydration | none | 10 | 45.5 | 15 | 31.9 |
| | 1 to 5% | 5 | 22.7 | 4 | 8.5 |
| | more than 5 % | 7 | 31.8 | 28 | 59.6 |

WT=Wild Type
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 45 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G2 type (ATP cohort for efficacy)**

| | | HRV N' = 42 | | Placebo N' = 107 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.8 | - | 9.5 | - |
| | SD | 3.8 | - | 4.7 | - |
| | Median | 8.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 36 | 85.7 | 66 | 61.7 |
| | 5 | 4 | 9.5 | 15 | 14.0 |
| | more than 5 days | 2 | 4.8 | 26 | 24.3 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 5 | 11.9 | 16 | 15.0 |
| | 4 to 5 | 22 | 52.4 | 42 | 39.3 |
| | more than 5 | 15 | 35.7 | 49 | 45.8 |
| Duration of vomiting (days) | 0 day | 23 | 54.8 | 42 | 39.3 |
| | 1 day | 8 | 19.0 | 30 | 28.0 |
| | 2 days | 9 | 21.4 | 17 | 15.9 |
| | more than 2 days | 2 | 4.8 | 18 | 16.8 |
| Max number of episodes of vomiting /day | 0 | 23 | 54.8 | 42 | 39.3 |
| | 1 | 4 | 9.5 | 15 | 14.0 |
| | 2 to 4 | 15 | 35.7 | 39 | 36.4 |
| | more than 4 | 0 | 0.0 | 11 | 10.3 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 11 | 26.2 | 29 | 27.1 |
| | 36.6 to 37.9°C | 20 | 47.6 | 43 | 40.2 |
| | 38.0 to 38.4°C | 7 | 16.7 | 12 | 11.2 |
| | more than 38.4°C | 4 | 9.5 | 23 | 21.5 |
| Treatment | none | 23 | 54.8 | 53 | 49.5 |
| | rehydration | 16 | 38.1 | 41 | 38.3 |
| | hospitalization | 3 | 7.1 | 13 | 12.1 |
| Dehydration | none | 23 | 54.8 | 53 | 49.5 |
| | 1 to 5% | 6 | 14.3 | 12 | 11.2 |
| | more than 5 % | 13 | 31.0 | 42 | 39.3 |

N' = number of RV GE episodes reported in each group
n/% = number/percentage of specified symptom reported in each group among N'
Value= value of the considered parameter
SD= standard deviation
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 46 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G3 type (ATP cohort for efficacy)**

| | | HRV N' = 1 | | Placebo N' = 12 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 4.0 | - | 8.8 | - |
| | SD | 0.0 | - | 4.3 | - |
| | Median | 4.0 | - | 8.5 | - |
| | Minimum | 4.0 | - | 2.0 | - |
| | Maximum | 4.0 | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 8 | 66.7 |
| | 5 | 0 | 0.0 | 1 | 8.3 |
| | more than 5 days | 0 | 0.0 | 3 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 100 | 2 | 16.7 |
| | 4 to 5 | 0 | 0.0 | 6 | 50.0 |
| | more than 5 | 0 | 0.0 | 4 | 33.3 |
| Duration of vomiting (days) | 0 day | 0 | 0.0 | 5 | 41.7 |
| | 1 day | 1 | 100 | 2 | 16.7 |
| | 2 days | 0 | 0.0 | 4 | 33.3 |
| | more than 2 days | 0 | 0.0 | 1 | 8.3 |
| Max number of episodes of vomiting /day | 0 | 0 | 0.0 | 5 | 41.7 |
| | 1 | 1 | 100 | 4 | 33.3 |
| | 2 to 4 | 0 | 0.0 | 2 | 16.7 |
| | more than 4 | 0 | 0.0 | 1 | 8.3 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 100 | 4 | 33.3 |
| | 36.6 to 37.9°C | 0 | 0.0 | 5 | 41.7 |
| | 38.0 to 38.4°C | 0 | 0.0 | 1 | 8.3 |
| | more than 38.4°C | 0 | 0.0 | 2 | 16.7 |
| Treatment | none | 1 | 100 | 6 | 50.0 |
| | rehydration | 0 | 0.0 | 6 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 6 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 8.3 |
| | more than 5 % | 0 | 0.0 | 5 | 41.7 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 47 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By G9 type (ATP cohort for efficacy)**

| | | HRV N' = 1 | | Placebo N' = 5 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 4.0 | - | 10.6 | - |
| | SD | 0.0 | - | 4.0 | - |
| | Median | 4.0 | - | 12.0 | - |
| | Minimum | 4.0 | - | 5.0 | - |
| | Maximum | 4.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 3 | 60.0 |
| | 5 | 0 | 0.0 | 1 | 20.0 |
| | more than 5 days | 0 | 0.0 | 1 | 20.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 0 | 0.0 |
| | 4 to 5 | 1 | 100 | 3 | 60.0 |
| | more than 5 | 0 | 0.0 | 2 | 40.0 |
| Duration of vomiting (days) | 0 day | 1 | 100 | 2 | 40.0 |
| | 1 day | 0 | 0.0 | 1 | 20.0 |
| | 2 days | 0 | 0.0 | 2 | 40.0 |
| | more than 2 days | 0 | 0.0 | 0 | 0.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 100 | 2 | 40.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |
| | 2 to 4 | 0 | 0.0 | 3 | 60.0 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 0 | 0.0 |
| | 36.6 to 37.9°C | 1 | 100 | 4 | 80.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 1 | 20.0 |
| Treatment | none | 1 | 100 | 1 | 20.0 |
| | rehydration | 0 | 0.0 | 4 | 80.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 1 | 20.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 20.0 |
| | more than 5 % | 0 | 0.0 | 3 | 60.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 48 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 – By GX type (ATP cohort for efficacy)**

| | | HRV N' = 6 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.7 | - | 13.4 | - |
| | SD | 2.6 | - | 3.5 | - |
| | Median | 7.0 | - | 14.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 50.0 | 5 | 62.5 |
| | 5 | 2 | 33.3 | 2 | 25.0 |
| | more than 5 days | 1 | 16.7 | 1 | 12.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 12.5 |
| | 4 to 5 | 4 | 66.7 | 1 | 12.5 |
| | more than 5 | 2 | 33.3 | 6 | 75.0 |
| Duration of vomiting (days) | 0 day | 4 | 66.7 | 1 | 12.5 |
| | 1 day | 1 | 16.7 | 2 | 25.0 |
| | 2 days | 1 | 16.7 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 5 | 62.5 |
| Max number of episodes of vomiting /day | 0 | 4 | 66.7 | 1 | 12.5 |
| | 1 | 1 | 16.7 | 1 | 12.5 |
| | 2 to 4 | 0 | 0.0 | 4 | 50.0 |
| | more than 4 | 1 | 16.7 | 2 | 25.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 16.7 | 1 | 12.5 |
| | 36.6 to 37.9°C | 5 | 83.3 | 4 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 3 | 37.5 |
| Treatment | none | 3 | 50.0 | 1 | 12.5 |
| | rehydration | 3 | 50.0 | 6 | 75.0 |
| | hospitalization | 0 | 0.0 | 1 | 12.5 |
| Dehydration | none | 3 | 50.0 | 1 | 12.5 |
| | 1 to 5% | 2 | 33.3 | 0 | 0.0 |
| | more than 5 % | 1 | 16.7 | 7 | 87.5 |

GX=G type unknown, but not vaccine strain
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 49 Characteristics of the GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | HRV N' = 1168 | | Placebo N' = 1238 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.9 | - | 7.1 | - |
| | SD | 3.8 | - | 4.1 | - |
| | Median | 6.0 | - | 6.0 | - |
| | Minimum | 2.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 5 | 0.4 | 4 | 0.3 |
| | 1 to 4 days | 854 | 73.1 | 865 | 69.9 |
| | 5 | 120 | 10.3 | 135 | 10.9 |
| | more than 5 days | 189 | 16.2 | 234 | 18.9 |
| Maximum number of looser than normal stools/day | 0 | 5 | 0.4 | 4 | 0.3 |
| | 1 to 3 | 207 | 17.7 | 219 | 17.7 |
| | 4 to 5 | 620 | 53.1 | 655 | 52.9 |
| | more than 5 | 336 | 28.8 | 360 | 29.1 |
| Duration of vomiting (days) | 0 day | 831 | 71.1 | 848 | 68.5 |
| | 1 day | 169 | 14.5 | 189 | 15.3 |
| | 2 days | 99 | 8.5 | 100 | 8.1 |
| | more than 2 days | 69 | 5.9 | 101 | 8.2 |
| Max number of episodes of vomiting /day | 0 | 831 | 71.1 | 848 | 68.5 |
| | 1 | 113 | 9.7 | 134 | 10.8 |
| | 2 to 4 | 191 | 16.4 | 202 | 16.3 |
| | more than 4 | 33 | 2.8 | 54 | 4.4 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 398 | 34.1 | 434 | 35.1 |
| | 36.6 to 37.9°C | 584 | 50.0 | 603 | 48.7 |
| | 38.0 to 38.4°C | 73 | 6.3 | 73 | 5.9 |
| | more than 38.4°C | 113 | 9.7 | 128 | 10.3 |
| Treatment | none | 719 | 61.6 | 754 | 60.9 |
| | rehydration | 403 | 34.5 | 404 | 32.6 |
| | hospitalization | 46 | 3.9 | 80 | 6.5 |
| Dehydration | none | 719 | 61.6 | 754 | 60.9 |
| | 1 to 5% | 181 | 15.5 | 172 | 13.9 |
| | more than 5 % | 268 | 22.9 | 312 | 25.2 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 50 Duration (in years) of efficacy follow-up period - from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | HRV N = 1575 | Placebo N = 1573 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 2104 | 2087 |
| | Mean | 1.34 | 1.33 |
| | Minimum | 0.01 | 0.01 |
| | Q1 | 1.28 | 1.27 |
| | Median | 1.38 | 1.38 |
| | Q3 | 1.46 | 1.46 |
| | Maximum | 1.56 | 1.56 |

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

## 11.4.1. Vaccine efficacy from 2 weeks after Dose 2 up to Visit 7

### 11.4.1.1. Vaccine efficacy against severe RV GE

**Table 51 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 21 | 1.3 | 0.8 | 2.0 | 72.0 | 54.1 | 83.6 | <0.001 |
| Placebo | 1573 | 75 | 4.8 | 3.8 | 5.9 | - | - | - | - |

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

**Table 52 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Severity using Vesikari scale** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| ≥11 | HRV | 1575 | 21 | 1.3 | 0.8 | 2.0 | 72.0 | 54.1 | 83.6 | <0.001 |
| | Placebo | 1573 | 75 | 4.8 | 3.8 | 5.9 | - | - | - | - |
| ≥12 | HRV | 1575 | 15 | 1.0 | 0.5 | 1.6 | 78.0 | 61.1 | 88.3 | <0.001 |
| | Placebo | 1573 | 68 | 4.3 | 3.4 | 5.4 | - | - | - | - |
| ≥13 | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 86.0 | 70.5 | 94.2 | <0.001 |
| | Placebo | 1573 | 57 | 3.6 | 2.8 | 4.7 | - | - | - | - |
| ≥14 | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 83.0 | 63.7 | 93.1 | <0.001 |
| | Placebo | 1573 | 47 | 3.0 | 2.2 | 4.0 | - | - | - | - |
| ≥15 | HRV | 1575 | 4 | 0.3 | 0.1 | 0.6 | 89.2 | 69.9 | 97.2 | <0.001 |
| | Placebo | 1573 | 37 | 2.4 | 1.7 | 3.2 | - | - | - | - |
| ≥16 | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 92.6 | 70.6 | 99.1 | <0.001 |
| | Placebo | 1573 | 27 | 1.7 | 1.1 | 2.5 | - | - | - | - |
| ≥17 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 67.2 | 100.0 | <0.001 |
| | Placebo | 1573 | 13 | 0.8 | 0.4 | 1.4 | - | - | - | - |
| ≥18 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 49.4 | 100.0 | 0.004 |
| | Placebo | 1573 | 9 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| ≥19 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| =20 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode with a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.4.1.2. Vaccine efficacy against any RV GE

**Table 53 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 70 | 4.4 | 3.5 | 5.6 | 58.1 | 44.3 | 68.8 | <0.001 |
| Placebo | 1573 | 167 | 10.6 | 9.1 | 12.2 | - | - | - | - |

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

### 11.4.1.3. Vaccine efficacy by G and P types

**Table 54 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1575 | 9 | 0.6 | 0.3 | 1.1 | 64.0 | 20.4 | 85.2 | 0.009 |
| | Placebo | 1573 | 25 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| G2 | HRV | 1575 | 11 | 0.7 | 0.3 | 1.2 | 74.5 | 49.6 | 88.1 | <0.001 |
| | Placebo | 1573 | 43 | 2.7 | 2.0 | 3.7 | - | - | - | - |
| G3 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| G9 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| GX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 83.4 | -37.2 | 99.6 | 0.125 |
| | Placebo | 1573 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| P4 | HRV | 1575 | 12 | 0.8 | 0.4 | 1.3 | 72.1 | 46.2 | 86.6 | <0.001 |
| | Placebo | 1573 | 43 | 2.7 | 2.0 | 3.7 | - | - | - | - |
| P8WT | HRV | 1575 | 9 | 0.6 | 0.3 | 1.1 | 71.0 | 37.6 | 87.9 | <0.001 |
| | Placebo | 1573 | 31 | 2.0 | 1.3 | 2.8 | - | - | - | - |
| PX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 0.1 | -7739.7 | 98.7 | 1.000 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1 WT | HRV | 1575 | 12 | 0.8 | 0.4 | 1.3 | 77.8 | 58.0 | 89.2 | <0.001 |
| | Placebo | 1573 | 54 | 3.4 | 2.6 | 4.5 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 55 Percentage of subjects reporting severe RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 60.1 | 5.3 | 84.8 | 0.035 |
| | Placebo | 1573 | 20 | 1.3 | 0.8 | 2.0 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 80.0 | -78.5 | 99.6 | 0.218 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G2+P4 | HRV | 1575 | 11 | 0.7 | 0.3 | 1.2 | 72.5 | 45.5 | 87.3 | <0.001 |
| | Placebo | 1573 | 40 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| G9+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |

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

## Table 56 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by RV type (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 52.2 | 19.0 | 72.6 | 0.005 |
| | Placebo | 1573 | 46 | 2.9 | 2.1 | 3.9 | - | - | - | - |
| G2 | HRV | 1575 | 42 | 2.7 | 1.9 | 3.6 | 60.1 | 42.3 | 72.8 | <0.001 |
| | Placebo | 1573 | 105 | 6.7 | 5.5 | 8.0 | - | - | - | - |
| G3 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 91.7 | 43.7 | 99.8 | 0.003 |
| | Placebo | 1573 | 12 | 0.8 | 0.4 | 1.3 | - | - | - | - |
| G9 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 80.0 | -78.5 | 99.6 | 0.218 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| GX | HRV | 1575 | 6 | 0.4 | 0.1 | 0.8 | 25.1 | -146.2 | 78.6 | 0.789 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| P4 | HRV | 1575 | 43 | 2.7 | 2.0 | 3.7 | 59.9 | 42.3 | 72.5 | <0.001 |
| | Placebo | 1573 | 107 | 6.8 | 5.6 | 8.2 | - | - | - | - |
| P8WT | HRV | 1575 | 25 | 1.6 | 1.0 | 2.3 | 57.7 | 31.4 | 74.6 | <0.001 |
| | Placebo | 1573 | 59 | 3.8 | 2.9 | 4.8 | - | - | - | - |
| P9 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| PX | HRV | 1575 | 4 | 0.3 | 0.1 | 0.6 | -299.5 | -19574.0 | 60.5 | 0.376 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1575 | 49 | 3.1 | 2.3 | 4.1 | 62.1 | 46.9 | 73.3 | <0.001 |
| | Placebo | 1573 | 129 | 8.2 | 6.9 | 9.7 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 57 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by combination of G and P type (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1575 | 20 | 1.3 | 0.8 | 2.0 | 47.4 | 7.4 | 71.0 | 0.024 |
| | Placebo | 1573 | 38 | 2.4 | 1.7 | 3.3 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 77.8 | -7.2 | 97.7 | 0.065 |
| | Placebo | 1573 | 9 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| G2+P4 | HRV | 1575 | 42 | 2.7 | 1.9 | 3.6 | 58.9 | 40.5 | 72.0 | <0.001 |
| | Placebo | 1573 | 102 | 6.5 | 5.3 | 7.8 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 60.2 | 100.0 | <0.001 |
| | Placebo | 1573 | 11 | 0.7 | 0.3 | 1.2 | - | - | - | - |
| G9+P8WT | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 80.0 | -78.5 | 99.6 | 0.218 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |

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

## Table 58 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 70 | 2063.29 | 0.034 | 0.027 | 0.043 | 0.051 | 0.036 | 0.067 |
| Placebo | 1573 | 167 | 1966.79 | 0.085 | 0.073 | 0.099 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1575 | 22 | 2095.16 | 0.011 | 0.007 | 0.016 | 0.012 | 0.004 | 0.020 |
| Placebo | 1573 | 46 | 2061.90 | 0.022 | 0.017 | 0.030 | . | . | . |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | |
| HRV | 1575 | 49 | 2071.51 | 0.024 | 0.018 | 0.031 | 0.041 | 0.028 | 0.055 |
| Placebo | 1573 | 129 | 1987.90 | 0.065 | 0.055 | 0.077 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 21 | 2092.32 | 0.010 | 0.007 | 0.015 | 0.027 | 0.018 | 0.037 |
| Placebo | 1573 | 75 | 2038.88 | 0.037 | 0.029 | 0.046 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1575 | 9 | 2100.84 | 0.004 | 0.002 | 0.008 | 0.008 | 0.002 | 0.014 |
| Placebo | 1573 | 25 | 2074.80 | 0.012 | 0.008 | 0.018 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1575 | 12 | 2095.16 | 0.006 | 0.003 | 0.010 | 0.021 | 0.013 | 0.029 |
| Placebo | 1573 | 54 | 2048.62 | 0.026 | 0.020 | 0.034 | . | . | . |

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

**Table 59 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 by Cox method (ATP cohort for efficacy)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 70 | 2063.29 | 0.03 | 0.03 | 0.04 | 60.00 | 47.12 | 69.74 | <0.001 |
| Placebo | 1573 | 167 | 1966.79 | 0.08 | 0.07 | 0.10 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1575 | 22 | 2095.16 | 0.01 | 0.01 | 0.02 | 53.15 | 22.13 | 71.81 | 0.003 |
| Placebo | 1573 | 46 | 2061.90 | 0.02 | 0.02 | 0.03 | - | - | - | - |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | | |
| HRV | 1575 | 49 | 2071.51 | 0.02 | 0.02 | 0.03 | 63.41 | 49.16 | 73.67 | <0.001 |
| Placebo | 1573 | 129 | 1987.90 | 0.06 | 0.05 | 0.08 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 21 | 2092.32 | 0.01 | 0.01 | 0.02 | 72.79 | 55.85 | 83.23 | <0.001 |
| Placebo | 1573 | 75 | 2038.88 | 0.04 | 0.03 | 0.05 | - | - | - | - |
| **Severe RVGE of G1WT** | | | | | | | | | | |
| HRV | 1575 | 9 | 2100.84 | 0.00 | 0.00 | 0.01 | 64.64 | 24.25 | 83.49 | 0.007 |
| Placebo | 1573 | 25 | 2074.80 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1WT** | | | | | | | | | | |
| HRV | 1575 | 12 | 2095.16 | 0.01 | 0.00 | 0.01 | 78.25 | 59.34 | 88.36 | <0.001 |
| Placebo | 1573 | 54 | 2048.62 | 0.03 | 0.02 | 0.03 | - | - | - | - |

WT=Wild type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)

### 11.4.1.4. Vaccine efficacy against hospitalisation due to RV GE

**Table 60 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 4 | 0.3 | 0.1 | 0.6 | 81.0 | 43.6 | 95.3 | <0.001 |
| Placebo | 1573 | 21 | 1.3 | 0.8 | 2.0 | - | - | - | - |

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

**Table 61 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 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 33 | 2.1 | 1.4 | 2.9 | 66.4 | 49.6 | 78.1 | <0.001 |
| Placebo | 1573 | 98 | 6.2 | 5.1 | 7.5 | - | - | - | - |

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

### 11.4.1.5. Vaccine efficacy against all cause GE

**Table 62 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 728 | 46.2 | 43.7 | 48.7 | 4.2 | -6.2 | 13.6 | 0.422 |
| Placebo | 1573 | 759 | 48.3 | 45.8 | 50.8 | - | - | - | - |

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

**Table 63 Percentage of subjects reporting all cause of severe GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 187 | 11.9 | 10.3 | 13.6 | 9.3 | -11.1 | 26.0 | 0.357 |
| Placebo | 1573 | 206 | 13.1 | 11.5 | 14.9 | - | - | - | - |

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

**Table 64 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 43 | 2.7 | 2.0 | 3.7 | 41.2 | 13.1 | 60.6 | 0.007 |
| Placebo | 1573 | 73 | 4.6 | 3.7 | 5.8 | - | - | - | - |

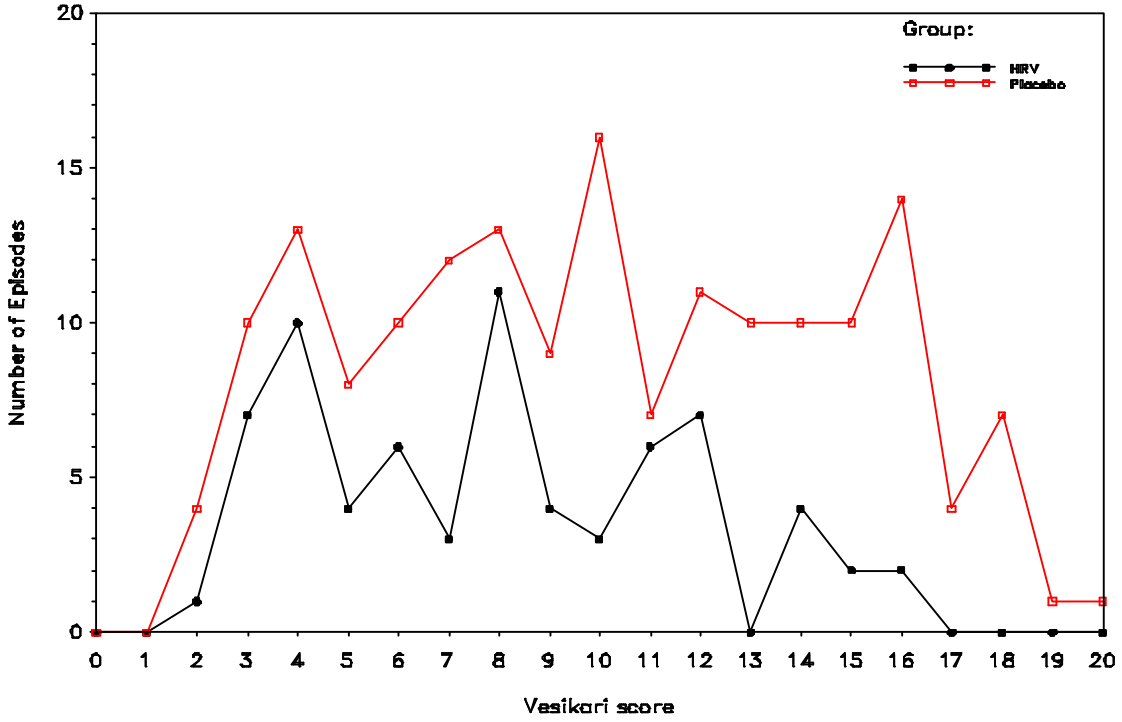
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 65 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 345 | 21.9 | 19.9 | 24.0 | 7.9 | -6.9 | 20.6 | 0.289 |
| Placebo | 1573 | 374 | 23.8 | 21.7 | 26.0 | - | - | - | - |

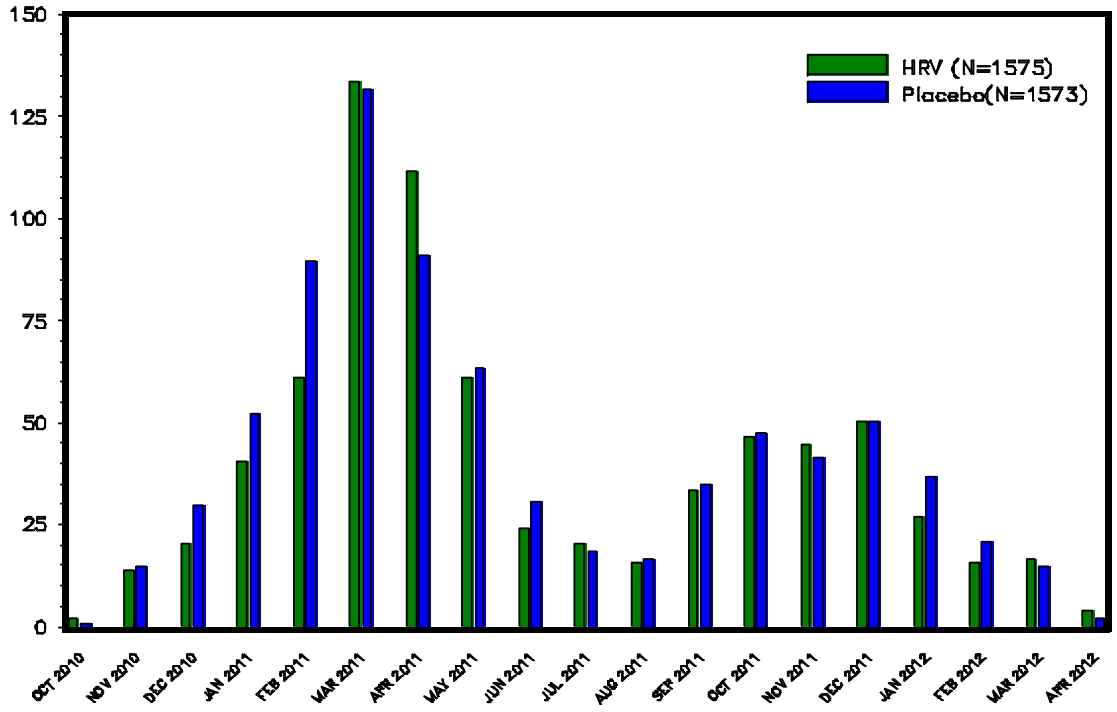
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 1 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



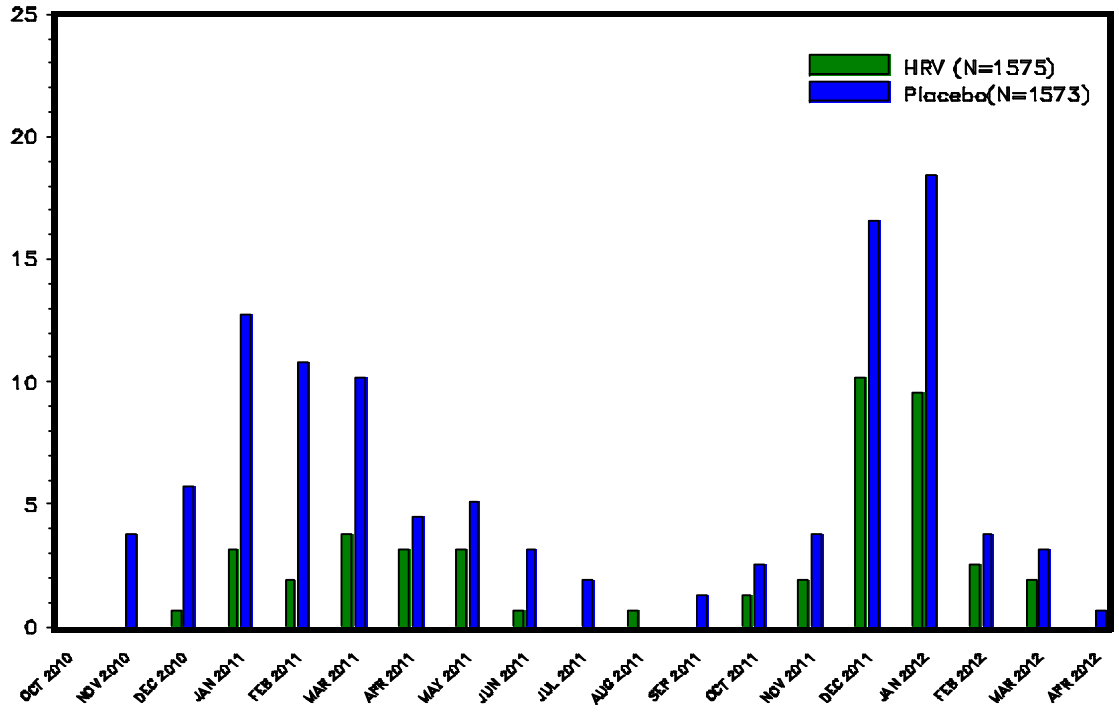

X axis = Score for each episodes computed based on the Vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 2** **Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 7 for HRV group and placebo group (ATP cohort for efficacy)**



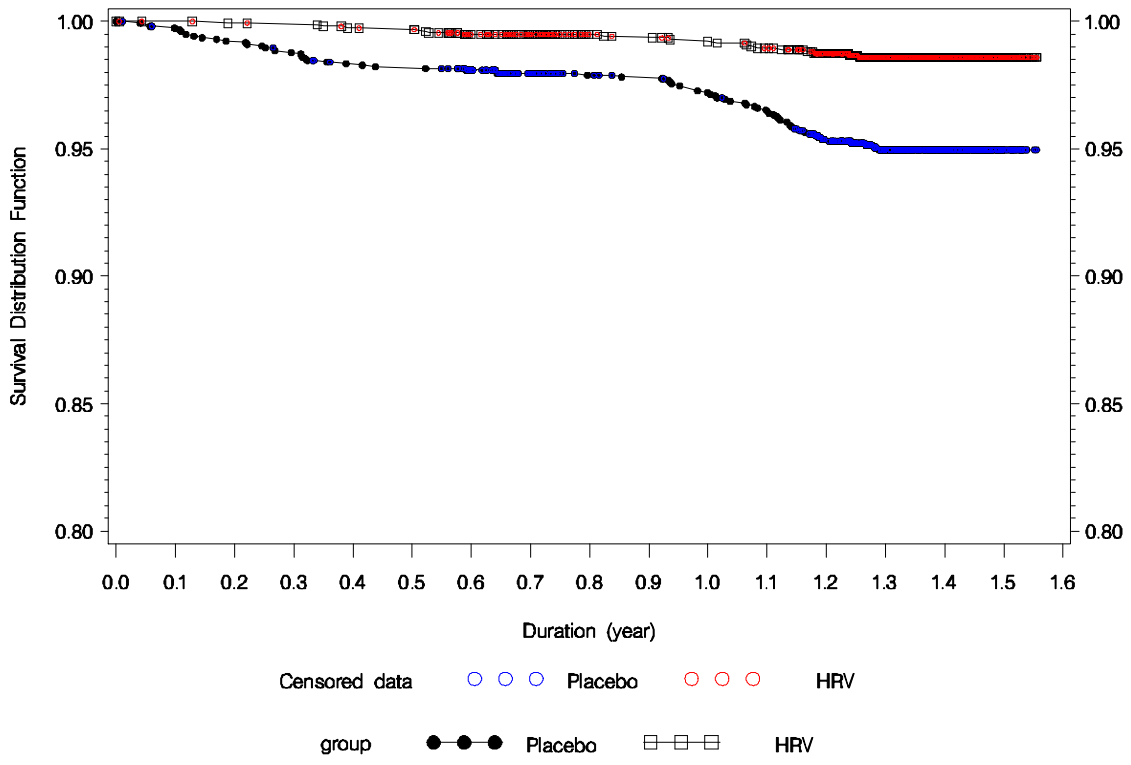

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 3** **Seasonal distribution of RVGE episodes reported from 2 weeks after Dose 2 up to Visit 7 for HRV group and placebo group (ATP cohort for efficacy)**



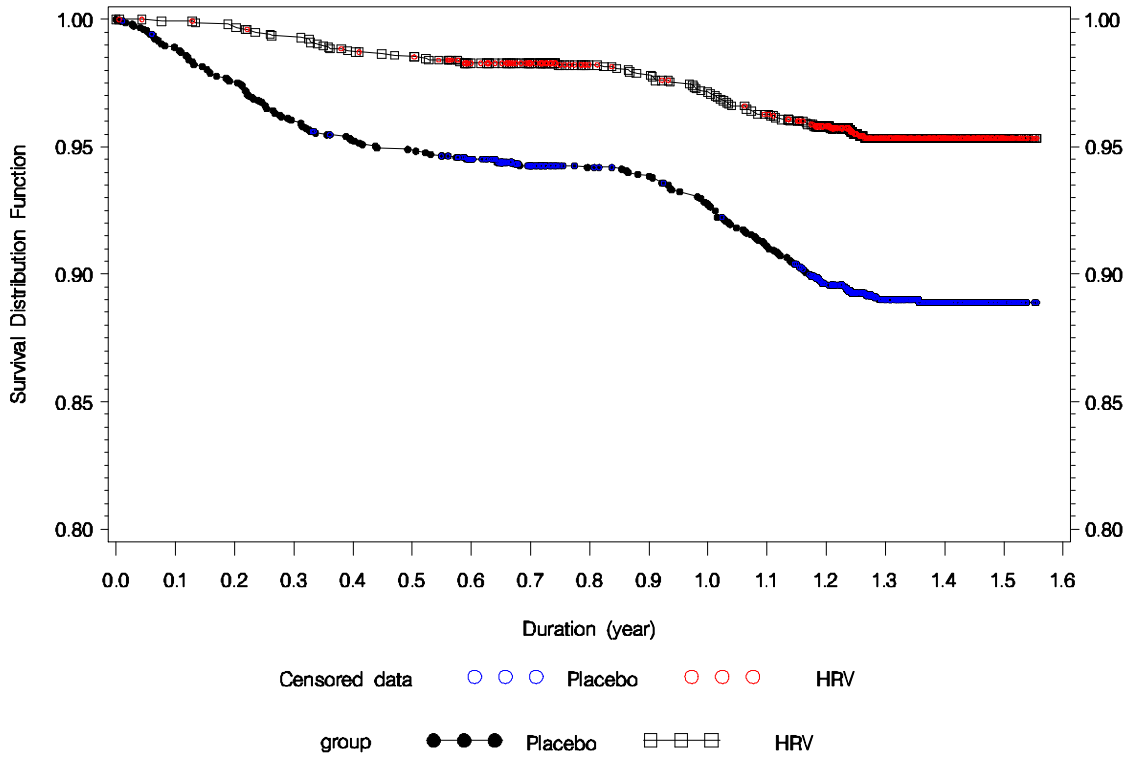

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 4 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



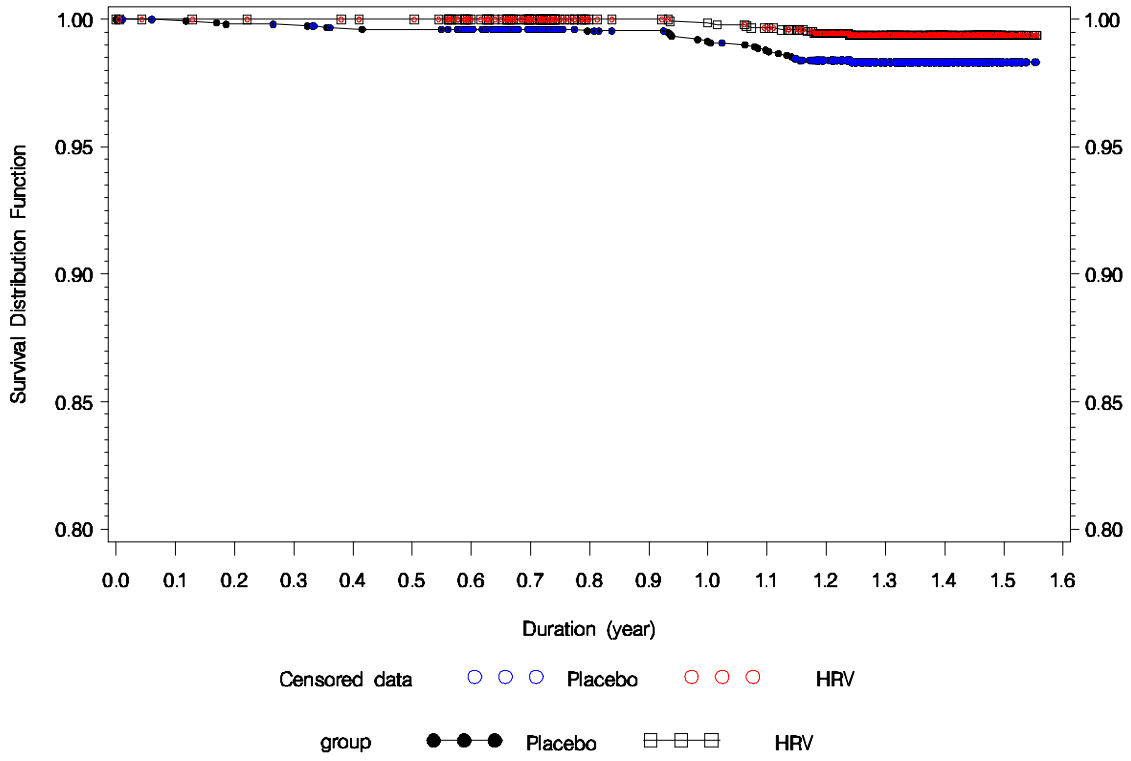

Y-axis has been cut at 0.8

**Figure 5 The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



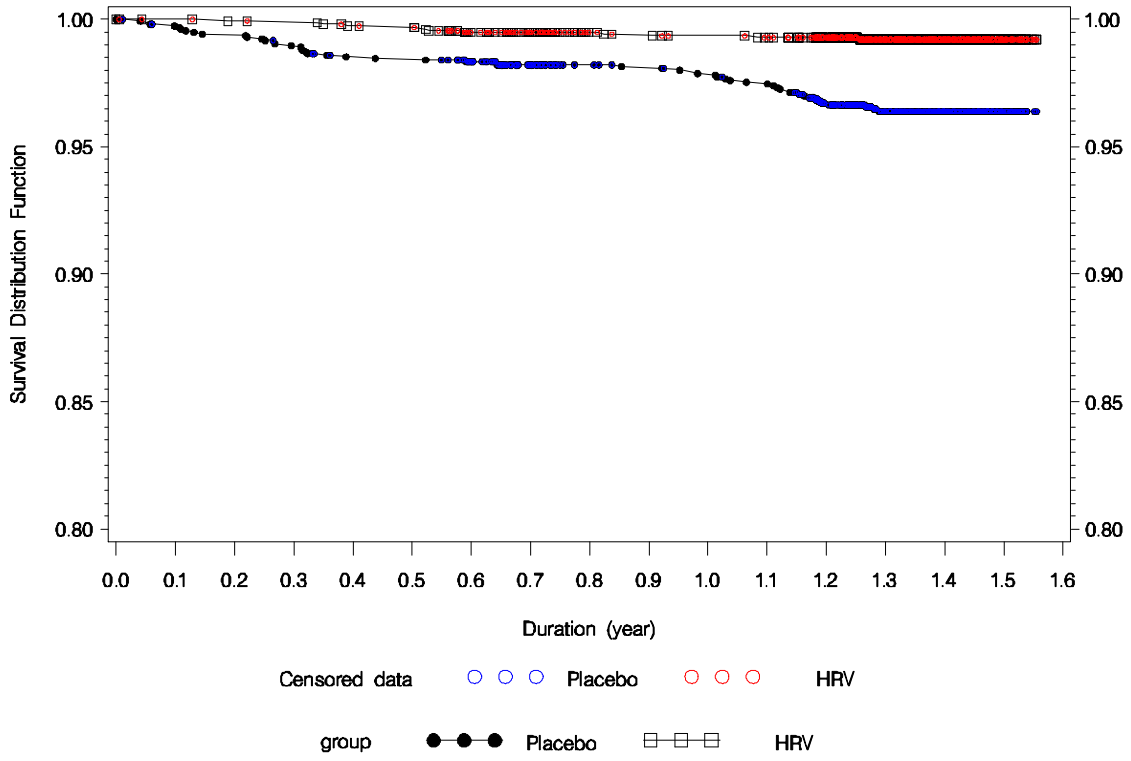

Y-axis has been cut at 0.8

**Figure 6 The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



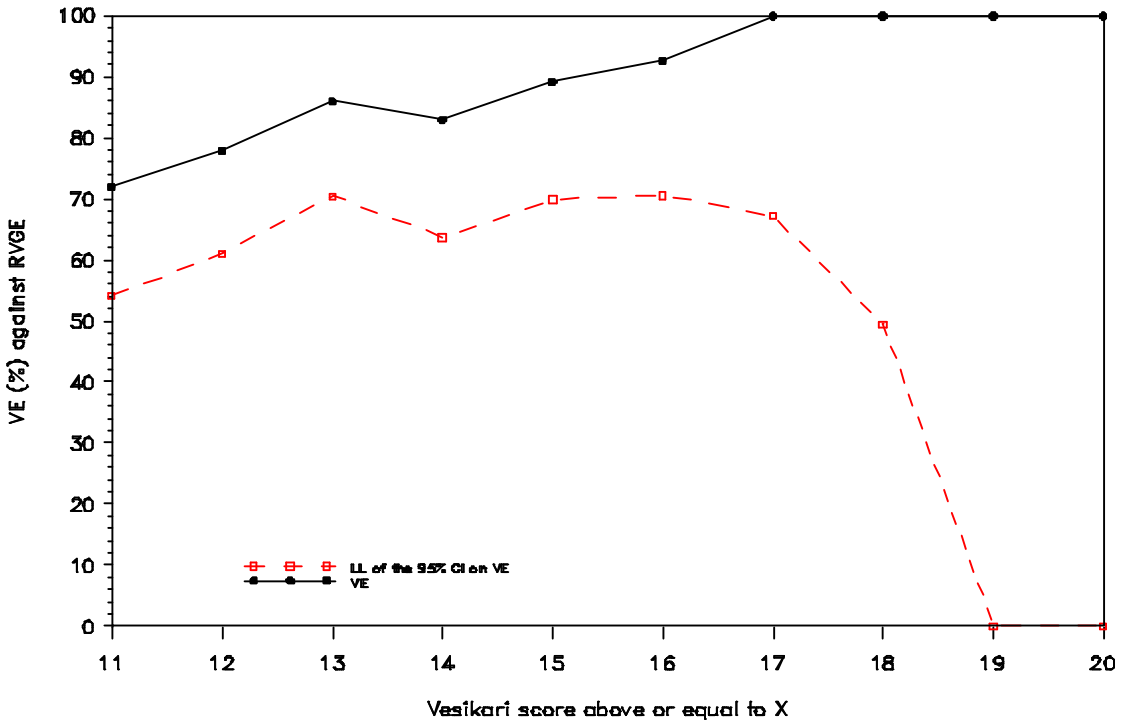

Y-axis has been cut at 0.8

**Figure 7** **The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**



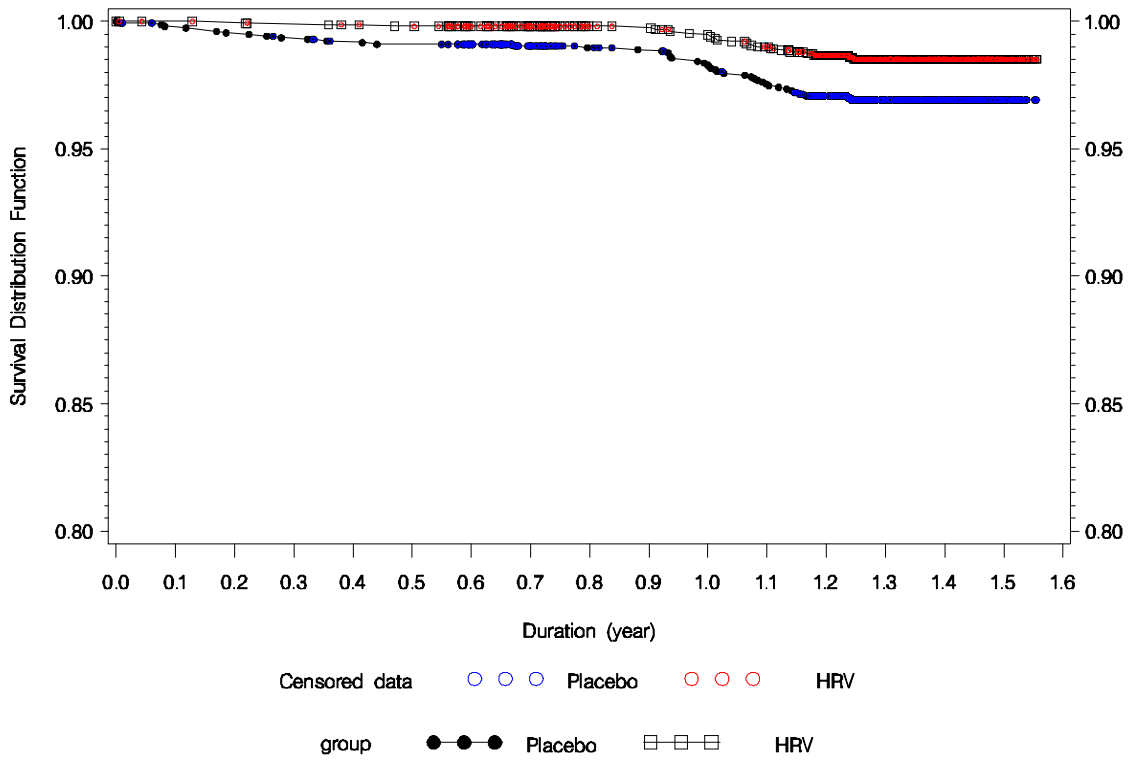

Y-axis has been cut at 0.8

**Figure 8** **Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from 2 weeks post dose 2 to visit 7 (ATP cohort for efficacy)**



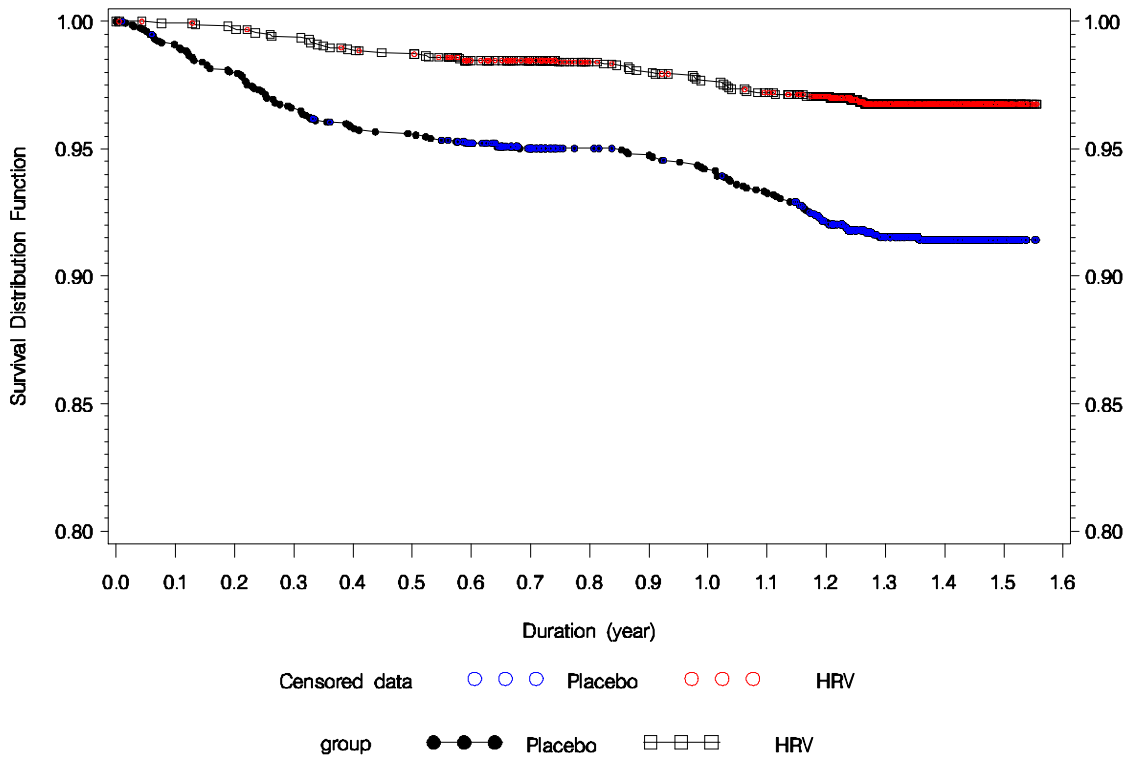

Y-axis has been cut at 0
X-axis has been cut at 11
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 9 The Kaplan Meier curve for any RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

**Figure 10 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 7 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

### 11.4.1.6. Characterization of GE episodes from 2 weeks after Dose 2 up to Visit 6

**Table 66 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | HRV N = 1575 | | Placebo N = 1573 | | Total N = 3148 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 997 | 63.3 | 956 | 60.8 | 1953 | 62.0 |
| | 1 | 425 | 27.0 | 452 | 28.7 | 877 | 27.9 |
| | 2 | 102 | 6.5 | 114 | 7.2 | 216 | 6.9 |
| | 3 | 38 | 2.4 | 31 | 2.0 | 69 | 2.2 |
| | 4 | 7 | 0.4 | 16 | 1.0 | 23 | 0.7 |
| | 5 | 5 | 0.3 | 3 | 0.2 | 8 | 0.3 |
| | 7 | 1 | 0.1 | 1 | 0.1 | 2 | 0.1 |
| | Any | 578 | 36.7 | 617 | 39.2 | 1195 | 38.0 |
| RVGE | 0 | 1548 | 98.3 | 1483 | 94.3 | 3031 | 96.3 |
| | 1 | 27 | 1.7 | 88 | 5.6 | 115 | 3.7 |
| | 2 | 0 | 0.0 | 2 | 0.1 | 2 | 0.1 |
| | Any | 27 | 1.7 | 90 | 5.7 | 117 | 3.7 |
| Severe GE | 0 | 1454 | 92.3 | 1453 | 92.4 | 2907 | 92.3 |
| | 1 | 113 | 7.2 | 109 | 6.9 | 222 | 7.1 |
| | 2 | 6 | 0.4 | 10 | 0.6 | 16 | 0.5 |
| | 3 | 2 | 0.1 | 1 | 0.1 | 3 | 0.1 |
| | Any | 121 | 7.7 | 120 | 7.6 | 241 | 7.7 |
| Severe RVGE | 0 | 1567 | 99.5 | 1541 | 98.0 | 3108 | 98.7 |
| | 1 | 8 | 0.5 | 32 | 2.0 | 40 | 1.3 |
| | Any | 8 | 0.5 | 32 | 2.0 | 40 | 1.3 |

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

**Table 67 Number of GE episodes reported from 2 weeks after Dose 2 up to Visit 6 by severity using the 20-point Vesikari scale (ATP cohort for efficacy)**

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| **Event** | **Severity using 20 point Vesikari scale** | **n** | **%** | **n** | **%** |
| GE | Mild (1-6) | 451 | 56.2 | 499 | 58.1 |
| | Moderate (7-10) | 221 | 27.5 | 227 | 26.4 |
| | Severe (≥11) | 131 | 16.3 | 132 | 15.4 |
| | Unknown | 0 | 0.0 | 1 | 0.1 |
| | Any | 803 | 100 | 858 | 99.9 |
| RVGE | Mild (1-6) | 11 | 40.7 | 29 | 31.5 |
| | Moderate (7-10) | 8 | 29.6 | 31 | 33.7 |
| | Severe (≥11) | 8 | 29.6 | 32 | 34.8 |
| | Any | 27 | 100 | 92 | 100 |

HRV = HRV
Placebo = Placebo
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

## Table 68 Percentage of GE episodes with no available stool results from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| | HRV N' = 803 | | Placebo N' = 859 | | Total N' = 1662 | |
|---|---|---|---|---|---|---|
| **Categories** | **n** | **%** | **n** | **%** | **n** | **%** |
| No stool results available | 46 | 5.7 | 48 | 5.6 | 94 | 5.7 |
| no stools collected | 46 | 5.7 | 48 | 5.6 | 94 | 5.7 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 69 Percentage of subjects with RV GE episodes from 2 weeks after Dose 2 up to Visit 6 by G and P type (ATP cohort for efficacy)

| Serotype | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| Any | 27 | 1.7 | 90 | 5.7 |
| G1 WT | 3 | 0.2 | 15 | 1.0 |
| G2 | 22 | 1.4 | 68 | 4.3 |
| G3 | 0 | 0.0 | 8 | 0.5 |
| G9 | 0 | 0.0 | 1 | 0.1 |
| GX | 2 | 0.1 | 2 | 0.1 |
| P4 | 22 | 1.4 | 67 | 4.3 |
| P8 WT | 3 | 0.2 | 23 | 1.5 |
| PX | 3 | 0.2 | 1 | 0.1 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 70 Percentage of subjects with severe RV GE episodes from 2 weeks after Dose 2 up to Visit 6 by G and P type (ATP cohort for efficacy)

| | HRV N = 1575 | | Placebo N = 1573 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 8 | 0.5 | 32 | 2.0 |
| G1 WT | 0 | 0.0 | 6 | 0.4 |
| G2 | 7 | 0.4 | 27 | 1.7 |
| G3 | 0 | 0.0 | 2 | 0.1 |
| GX | 1 | 0.1 | 0 | 0.0 |
| P4 | 7 | 0.4 | 25 | 1.6 |
| P8 WT | 1 | 0.1 | 7 | 0.4 |
| PX | 1 | 0.1 | 1 | 0.1 |

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 severe RV GE episode whatever the serotype
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 71 Number of RV GE episodes reported from 2 weeks after Dose 2 up to Visit 6, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=27 | | Placebo N'=92 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 3 | 3.26 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 1.09 |
| G1WT+P8WT | 2 | 7.41 | 12 | 13.04 |
| G1WT+PX | 1 | 3.70 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.09 |
| G2+P4 | 21 | 77.78 | 64 | 69.57 |
| G2+P4+P8WT | 1 | 3.70 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.09 |
| G3+P8WT | 0 | 0.00 | 7 | 7.61 |
| G9+P8WT | 0 | 0.00 | 1 | 1.09 |
| GX | 0 | 0.00 | 1 | 1.09 |
| GX+P8WT | 0 | 0.00 | 1 | 1.09 |
| GX+PX | 2 | 7.41 | 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 2 of HRV vaccine or placebo up to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 72 Number of severe RV GE episodes reported from 2 weeks after Dose 2 up to Visit 6, by G and P type (ATP cohort for efficacy)

| Serotype | HRV N'=8 | | Placebo N'=32 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 3.13 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 3.13 |
| G1WT+P8WT | 0 | 0.00 | 4 | 12.50 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 3.13 |
| G2+P4 | 6 | 75.00 | 23 | 71.88 |
| G2+P4+P8WT | 1 | 12.50 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 3.13 |
| G3+P8WT | 0 | 0.00 | 1 | 3.13 |
| GX+PX | 1 | 12.50 | 0 | 0.00 |

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 severe RV GE episodes reported from 2 weeks after dose 2 of HRV vaccine or placebo up to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 73 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | HRV N' = 27 | | Placebo N' = 92 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.0 | - | 8.9 | - |
| | SD | 4.0 | - | 4.3 | - |
| | Median | 8.0 | - | 8.5 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 22 | 81.5 | 57 | 62.0 |
| | 5 | 3 | 11.1 | 13 | 14.1 |
| | more than 5 days | 2 | 7.4 | 22 | 23.9 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 4 | 14.8 | 14 | 15.2 |
| | 4 to 5 | 11 | 40.7 | 36 | 39.1 |
| | more than 5 | 12 | 44.4 | 42 | 45.7 |
| Duration of vomiting (days) | 0 day | 16 | 59.3 | 45 | 48.9 |
| | 1 day | 4 | 14.8 | 19 | 20.7 |
| | 2 days | 5 | 18.5 | 13 | 14.1 |
| | more than 2 days | 2 | 7.4 | 15 | 16.3 |
| Max number of episodes of vomiting /day | 0 | 16 | 59.3 | 45 | 48.9 |
| | 1 | 2 | 7.4 | 12 | 13.0 |
| | 2 to 4 | 8 | 29.6 | 27 | 29.3 |
| | more than 4 | 1 | 3.7 | 8 | 8.7 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 6 | 22.2 | 30 | 32.6 |
| | 36.6 to 37.9°C | 13 | 48.1 | 40 | 43.5 |
| | 38.0 to 38.4°C | 6 | 22.2 | 12 | 13.0 |
| | more than 38.4°C | 2 | 7.4 | 10 | 10.9 |
| Treatment | none | 15 | 55.6 | 46 | 50.0 |
| | rehydration | 10 | 37.0 | 32 | 34.8 |
| | hospitalization | 2 | 7.4 | 14 | 15.2 |
| Dehydration | none | 15 | 55.6 | 46 | 50.0 |
| | 1 to 5% | 3 | 11.1 | 11 | 12.0 |
| | more than 5 % | 9 | 33.3 | 35 | 38.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 74 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By G1WT type (ATP cohort for efficacy)**

| | | HRV N' = 3 | | Placebo N' = 16 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.0 | - | 8.6 | - |
| | SD | 3.6 | - | 3.4 | - |
| | Median | 5.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 3.0 | - |
| | Maximum | 10.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 100 | 10 | 62.5 |
| | 5 | 0 | 0.0 | 4 | 25.0 |
| | more than 5 days | 0 | 0.0 | 2 | 12.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 33.3 | 0 | 0.0 |
| | 4 to 5 | 1 | 33.3 | 11 | 68.8 |
| | more than 5 | 1 | 33.3 | 5 | 31.3 |
| Duration of vomiting (days) | 0 day | 3 | 100 | 8 | 50.0 |
| | 1 day | 0 | 0.0 | 5 | 31.3 |
| | 2 days | 0 | 0.0 | 2 | 12.5 |
| | more than 2 days | 0 | 0.0 | 1 | 6.3 |
| Max number of episodes of vomiting /day | 0 | 3 | 100 | 8 | 50.0 |
| | 1 | 0 | 0.0 | 2 | 12.5 |
| | 2 to 4 | 0 | 0.0 | 6 | 37.5 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 4 | 25.0 |
| | 36.6 to 37.9°C | 1 | 33.3 | 8 | 50.0 |
| | 38.0 to 38.4°C | 1 | 33.3 | 3 | 18.8 |
| | more than 38.4°C | 1 | 33.3 | 1 | 6.3 |
| Treatment | none | 2 | 66.7 | 8 | 50.0 |
| | rehydration | 1 | 33.3 | 4 | 25.0 |
| | hospitalization | 0 | 0.0 | 4 | 25.0 |
| Dehydration | none | 2 | 66.7 | 8 | 50.0 |
| | 1 to 5% | 1 | 33.3 | 2 | 12.5 |
| | more than 5 % | 0 | 0.0 | 6 | 37.5 |

WT =Wild Type
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 75 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By G2 type (ATP cohort for efficacy)**

| | | HRV N' = 22 | | Placebo N' = 70 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.2 | - | 9.2 | - |
| | SD | 4.0 | - | 4.6 | - |
| | Median | 8.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 19 | 86.4 | 42 | 60.0 |
| | 5 | 2 | 9.1 | 8 | 11.4 |
| | more than 5 days | 1 | 4.5 | 20 | 28.6 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 3 | 13.6 | 12 | 17.1 |
| | 4 to 5 | 9 | 40.9 | 25 | 35.7 |
| | more than 5 | 10 | 45.5 | 33 | 47.1 |
| Duration of vomiting (days) | 0 day | 12 | 54.5 | 33 | 47.1 |
| | 1 day | 4 | 18.2 | 14 | 20.0 |
| | 2 days | 4 | 18.2 | 11 | 15.7 |
| | more than 2 days | 2 | 9.1 | 12 | 17.1 |
| Max number of episodes of vomiting /day | 0 | 12 | 54.5 | 33 | 47.1 |
| | 1 | 2 | 9.1 | 6 | 8.6 |
| | 2 to 4 | 8 | 36.4 | 23 | 32.9 |
| | more than 4 | 0 | 0.0 | 8 | 11.4 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 6 | 27.3 | 22 | 31.4 |
| | 36.6 to 37.9°C | 10 | 45.5 | 29 | 41.4 |
| | 38.0 to 38.4°C | 5 | 22.7 | 10 | 14.3 |
| | more than 38.4°C | 1 | 4.5 | 9 | 12.9 |
| Treatment | none | 11 | 50.0 | 35 | 50.0 |
| | rehydration | 9 | 40.9 | 24 | 34.3 |
| | hospitalization | 2 | 9.1 | 11 | 15.7 |
| Dehydration | none | 11 | 50.0 | 35 | 50.0 |
| | 1 to 5% | 2 | 9.1 | 7 | 10.0 |
| | more than 5 % | 9 | 40.9 | 28 | 40.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 76 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By G3 type (ATP cohort for efficacy)**

| | | HRV N' = 0 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | - | - | 8.8 | - |
| | SD | - | - | 4.2 | - |
| | Median | - | - | 8.5 | - |
| | Minimum | - | - | 2.0 | - |
| | Maximum | - | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | - | - | 0 | 0.0 |
| | 1 to 4 days | - | - | 5 | 62.5 |
| | 5 | - | - | 1 | 12.5 |
| | more than 5 days | - | - | 2 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | - | - | 0 | 0.0 |
| | 1 to 3 | - | - | 1 | 12.5 |
| | 4 to 5 | - | - | 4 | 50.0 |
| | more than 5 | - | - | 3 | 37.5 |
| Duration of vomiting (days) | 0 day | - | - | 3 | 37.5 |
| | 1 day | - | - | 2 | 25.0 |
| | 2 days | - | - | 2 | 25.0 |
| | more than 2 days | - | - | 1 | 12.5 |
| Max number of episodes of vomiting /day | 0 | - | - | 3 | 37.5 |
| | 1 | - | - | 3 | 37.5 |
| | 2 to 4 | - | - | 1 | 12.5 |
| | more than 4 | - | - | 1 | 12.5 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | - | - | 3 | 37.5 |
| | 36.6 to 37.9°C | - | - | 4 | 50.0 |
| | 38.0 to 38.4°C | - | - | 0 | 0.0 |
| | more than 38.4°C | - | - | 1 | 12.5 |
| Treatment | none | - | - | 4 | 50.0 |
| | rehydration | - | - | 4 | 50.0 |
| | hospitalization | - | - | 0 | 0.0 |
| Dehydration | none | - | - | 4 | 50.0 |
| | 1 to 5% | - | - | 1 | 12.5 |
| | more than 5 % | - | - | 3 | 37.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 77 Characteristics of the RV GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 – By GX type (ATP cohort for efficacy)**

| | | HRV N' = 2 | | Placebo N' = 2 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.5 | - | 9.0 | - |
| | SD | 4.9 | - | 1.4 | - |
| | Median | 8.5 | - | 9.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 10.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 0 | 0.0 | 2 | 100 |
| | 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 days | 1 | 50.0 | 0 | 0.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 50.0 |
| | 4 to 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 | 1 | 50.0 | 1 | 50.0 |
| Duration of vomiting (days) | 0 day | 1 | 50.0 | 0 | 0.0 |
| | 1 day | 0 | 0.0 | 1 | 50.0 |
| | 2 days | 1 | 50.0 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 1 | 50.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 50.0 | 0 | 0.0 |
| | 1 | 0 | 0.0 | 1 | 50.0 |
| | 2 to 4 | 0 | 0.0 | 1 | 50.0 |
| | more than 4 | 1 | 50.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 1 | 50.0 |
| | 36.6 to 37.9°C | 2 | 100 | 1 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 0 | 0.0 |
| Treatment | none | 2 | 100 | 1 | 50.0 |
| | rehydration | 0 | 0.0 | 1 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 2 | 100 | 1 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 0 | 0.0 |
| | more than 5 % | 0 | 0.0 | 1 | 50.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain

**Table 78 Characteristics of the GE episodes (based on Vesikari scale) reported from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | HRV N' = 803 | | Placebo N' = 859 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.6 | - | 6.5 | - |
| | SD | 3.7 | - | 3.7 | - |
| | Median | 6.0 | - | 6.0 | - |
| | Minimum | 2.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 3 | 0.4 | 2 | 0.2 |
| | 1 to 4 days | 573 | 71.4 | 601 | 70.0 |
| | 5 | 84 | 10.5 | 78 | 9.1 |
| | more than 5 days | 143 | 17.8 | 178 | 20.7 |
| Maximum number of looser than normal stools/day | 0 | 3 | 0.4 | 2 | 0.2 |
| | 1 to 3 | 168 | 20.9 | 156 | 18.2 |
| | 4 to 5 | 406 | 50.6 | 463 | 53.9 |
| | more than 5 | 226 | 28.1 | 238 | 27.7 |
| Duration of vomiting (days) | 0 day | 607 | 75.6 | 650 | 75.7 |
| | 1 day | 93 | 11.6 | 107 | 12.5 |
| | 2 days | 58 | 7.2 | 48 | 5.6 |
| | more than 2 days | 45 | 5.6 | 54 | 6.3 |
| Max number of episodes of vomiting /day | 0 | 607 | 75.6 | 650 | 75.7 |
| | 1 | 66 | 8.2 | 79 | 9.2 |
| | 2 to 4 | 114 | 14.2 | 107 | 12.5 |
| | more than 4 | 16 | 2.0 | 23 | 2.7 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 309 | 38.5 | 352 | 41.0 |
| | 36.6 to 37.9°C | 373 | 46.5 | 378 | 44.0 |
| | 38.0 to 38.4°C | 49 | 6.1 | 54 | 6.3 |
| | more than 38.4°C | 72 | 9.0 | 75 | 8.7 |
| Treatment | none | 518 | 64.5 | 568 | 66.1 |
| | rehydration | 245 | 30.5 | 240 | 27.9 |
| | hospitalization | 40 | 5.0 | 51 | 5.9 |
| Dehydration | none | 518 | 64.5 | 568 | 66.1 |
| | 1 to 5% | 112 | 13.9 | 115 | 13.4 |
| | more than 5 % | 173 | 21.5 | 176 | 20.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 79 Duration (in years) of efficacy follow-up period - from 2 weeks after Dose 2 up to visit 6 (ATP cohort for efficacy)**

| | | HRV N = 1575 | Placebo N = 1573 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 1068 | 1063 |
| | Mean | 0.68 | 0.68 |
| | Minimum | 0.01 | 0.01 |
| | Q1 | 0.64 | 0.64 |
| | Median | 0.68 | 0.68 |
| | Q3 | 0.73 | 0.72 |
| | Maximum | 0.93 | 0.93 |

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

## 11.4.2. Vaccine efficacy from 2 weeks after Dose 2 up to Visit 6

### 11.4.2.1. Vaccine efficacy against severe RV GE

**Table 80 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 75.0 | 44.7 | 90.1 | <0.001 |
| Placebo | 1573 | 32 | 2.0 | 1.4 | 2.9 | - | - | - | - |

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

**Table 81 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from 2 weeks after dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Severity using Vesikari scale** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| ≥11 | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 75.0 | 44.7 | 90.1 | <0.001 |
| | Placebo | 1573 | 32 | 2.0 | 1.4 | 2.9 | - | - | - | - |
| ≥12 | HRV | 1575 | 6 | 0.4 | 0.1 | 0.8 | 78.6 | 47.3 | 92.8 | <0.001 |
| | Placebo | 1573 | 28 | 1.8 | 1.2 | 2.6 | - | - | - | - |
| ≥13 | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 85.0 | 49.5 | 97.1 | <0.001 |
| | Placebo | 1573 | 20 | 1.3 | 0.8 | 2.0 | - | - | - | - |
| ≥14 | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 77.0 | 16.1 | 95.8 | 0.021 |
| | Placebo | 1573 | 13 | 0.8 | 0.4 | 1.4 | - | - | - | - |
| ≥15 | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 77.8 | -7.2 | 97.7 | 0.065 |
| | Placebo | 1573 | 9 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| ≥16 | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 87.5 | 6.9 | 99.7 | 0.039 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| ≥17 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -51.3 | 100.0 | 0.125 |
| | Placebo | 1573 | 4 | 0.3 | 0.1 | 0.6 | - | - | - | - |
| ≥18 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -141.7 | 100.0 | 0.250 |
| | Placebo | 1573 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| ≥19 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| =20 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least one RV GE episode with a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
p_value=two-sided exact p_value conditional to the number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.4.2.2. Vaccine efficacy against any RV GE

**Table 82 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1575 | 27 | 1.7 | 1.1 | 2.5 | 70.0 | 53.5 | 81.3 | <0.001 |
| Placebo | 1573 | 90 | 5.7 | 4.6 | 7.0 | - | - | - | - |

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

### 11.4.2.3. Vaccine efficacy by G and P types

**Table 83 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RV GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by RV type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 15.2 | 100.0 | 0.031 |
| | Placebo | 1573 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| G2 | HRV | 1575 | 7 | 0.4 | 0.2 | 0.9 | 74.1 | 39.1 | 90.5 | <0.001 |
| | Placebo | 1573 | 27 | 1.7 | 1.1 | 2.5 | - | - | - | - |
| G3 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| GX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | Und. | Und. | Und. | 1.000 |
| | Placebo | 1573 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |
| P4 | HRV | 1575 | 7 | 0.4 | 0.2 | 0.9 | 72.0 | 33.5 | 89.8 | 0.002 |
| | Placebo | 1573 | 25 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| P8WT | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 85.7 | -11.1 | 99.7 | 0.070 |
| | Placebo | 1573 | 7 | 0.4 | 0.2 | 0.9 | - | - | - | - |
| PX | HRV | 1575 | 1 | 0.1 | 0.0 | 0.4 | 0.1 | -7739.7 | 98.7 | 1.000 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1575 | 8 | 0.5 | 0.2 | 1.0 | 71.5 | 35.7 | 88.8 | 0.001 |
| | Placebo | 1573 | 28 | 1.8 | 1.2 | 2.6 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain
Und. = cannot be estimated

**Table 84 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by combination of G and P type (ATP cohort for efficacy)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -9.0 | 100.0 | 0.062 |
| | Placebo | 1573 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| G2+P4 | HRV | 1575 | 7 | 0.4 | 0.2 | 0.9 | 72.0 | 33.5 | 89.8 | 0.002 |
| | Placebo | 1573 | 25 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |

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

## Table 85 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by RV type (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 80.0 | 29.4 | 96.3 | 0.007 |
| | Placebo | 1573 | 15 | 1.0 | 0.5 | 1.6 | - | - | - | - |
| G2 | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 67.7 | 47.1 | 81.0 | <0.001 |
| | Placebo | 1573 | 68 | 4.3 | 3.4 | 5.4 | - | - | - | - |
| G3 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 41.5 | 100.0 | 0.008 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| G9 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| GX | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 0.1 | -1277.8 | 92.8 | 1.000 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| P4 | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 67.2 | 46.2 | 80.7 | <0.001 |
| | Placebo | 1573 | 67 | 4.3 | 3.3 | 5.4 | - | - | - | - |
| P8WT | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | 87.0 | 56.9 | 97.5 | <0.001 |
| | Placebo | 1573 | 23 | 1.5 | 0.9 | 2.2 | - | - | - | - |
| PX | HRV | 1575 | 3 | 0.2 | 0.0 | 0.6 | -199.6 | -15629.2 | 75.9 | 0.626 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1575 | 24 | 1.5 | 1.0 | 2.3 | 69.3 | 50.9 | 81.4 | <0.001 |
| | Placebo | 1573 | 78 | 5.0 | 3.9 | 6.2 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 86 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by combination of G and P types (ATP cohort for efficacy)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 84.6 | 32.1 | 98.3 | 0.007 |
| | Placebo | 1573 | 13 | 0.8 | 0.4 | 1.4 | - | - | - | - |
| G1WT+P4 | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -431.8 | 100.0 | 0.499 |
| | Placebo | 1573 | 2 | 0.1 | 0.0 | 0.5 | - | - | - | - |
| G2+P4 | HRV | 1575 | 22 | 1.4 | 0.9 | 2.1 | 67.2 | 46.2 | 80.7 | <0.001 |
| | Placebo | 1573 | 67 | 4.3 | 3.3 | 5.4 | - | - | - | - |
| G3+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 41.5 | 100.0 | 0.008 |
| | Placebo | 1573 | 8 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| G9+P8WT | HRV | 1575 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3795.0 | 100.0 | 0.999 |
| | Placebo | 1573 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |

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

## Table 87 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 27 | 1058.48 | 0.026 | 0.017 | 0.037 | 0.062 | 0.042 | 0.084 |
| Placebo | 1573 | 90 | 1025.32 | 0.088 | 0.071 | 0.108 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1575 | 3 | 1066.78 | 0.003 | 0.001 | 0.009 | 0.011 | 0.003 | 0.021 |
| Placebo | 1573 | 15 | 1056.32 | 0.014 | 0.009 | 0.024 | . | . | . |
| **Any RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1575 | 24 | 1059.46 | 0.023 | 0.015 | 0.034 | 0.053 | 0.034 | 0.073 |
| Placebo | 1573 | 78 | 1030.71 | 0.076 | 0.061 | 0.094 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.008 | 0.004 | 0.015 | 0.023 | 0.011 | 0.036 |
| Placebo | 1573 | 32 | 1050.22 | 0.030 | 0.022 | 0.043 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1575 | 0 | 1067.76 | 0 | Und. | Und. | 0.006 | Und. | Und. |
| Placebo | 1573 | 6 | 1060.24 | 0.006 | 0.003 | 0.013 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.008 | 0.004 | 0.015 | 0.019 | 0.008 | 0.032 |
| Placebo | 1573 | 28 | 1052.01 | 0.027 | 0.018 | 0.039 | . | . | . |

WT=Wild Type
N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(S) in each group
T(Year)= Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Risk difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner
Und. = cannot be estimated

**Table 88 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 by Cox method (ATP cohort for efficacy)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 27 | 1058.48 | 0.03 | 0.02 | 0.04 | 70.79 | 55.09 | 81.00 | <0.001 |
| Placebo | 1573 | 90 | 1025.32 | 0.09 | 0.07 | 0.11 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1575 | 3 | 1066.78 | 0.00 | 0.00 | 0.01 | 80.15 | 31.45 | 94.25 | 0.011 |
| Placebo | 1573 | 15 | 1056.32 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Any RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1575 | 24 | 1059.46 | 0.02 | 0.02 | 0.03 | 69.92 | 52.46 | 80.96 | <0.001 |
| Placebo | 1573 | 78 | 1030.71 | 0.08 | 0.06 | 0.09 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.01 | 0.00 | 0.02 | 75.27 | 46.34 | 88.60 | <0.001 |
| Placebo | 1573 | 32 | 1050.22 | 0.03 | 0.02 | 0.04 | - | - | - | - |
| **Severe RVGE of G1 WT** | | | | | | | | | | |
| HRV | 1575 | 0 | 1067.76 | 0.00 | Und. | Und. | 100.00 | Und. | 100.00 | 0.994 |
| Placebo | 1573 | 6 | 1060.24 | 0.01 | 0.00 | 0.01 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1575 | 8 | 1065.90 | 0.01 | 0.00 | 0.02 | 71.70 | 37.90 | 87.10 | 0.002 |
| Placebo | 1573 | 28 | 1052.01 | 0.03 | 0.02 | 0.04 | - | - | - | - |

WT=Wild Type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)
Und. = cannot be estimated

### 11.4.2.4. Vaccine efficacy against hospitalisation due to RV

**Table 89 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 2 | 0.1 | 0.0 | 0.5 | 85.7 | 37.9 | 98.4 | 0.004 |
| Placebo | 1573 | 14 | 0.9 | 0.5 | 1.5 | - | - | - | - |

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

**Table 90 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 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 12 | 0.8 | 0.4 | 1.3 | 73.9 | 50.0 | 87.4 | <0.001 |
| Placebo | 1573 | 46 | 2.9 | 2.1 | 3.9 | - | - | - | - |

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

### 11.4.2.5. Vaccine efficacy against all cause GE and severe GE

**Table 91 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 578 | 36.7 | 34.3 | 39.1 | 6.4 | -5.0 | 16.6 | 0.262 |
| Placebo | 1573 | 617 | 39.2 | 36.8 | 41.7 | - | - | - | - |

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

**Table 92 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 121 | 7.7 | 6.4 | 9.1 | -0.7 | -30.7 | 22.4 | 1.000 |
| Placebo | 1573 | 120 | 7.6 | 6.4 | 9.1 | - | - | - | - |

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

**Table 93 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 37 | 2.3 | 1.7 | 3.2 | 21.4 | -23.6 | 50.3 | 0.323 |
| Placebo | 1573 | 47 | 3.0 | 2.2 | 4.0 | - | - | - | - |

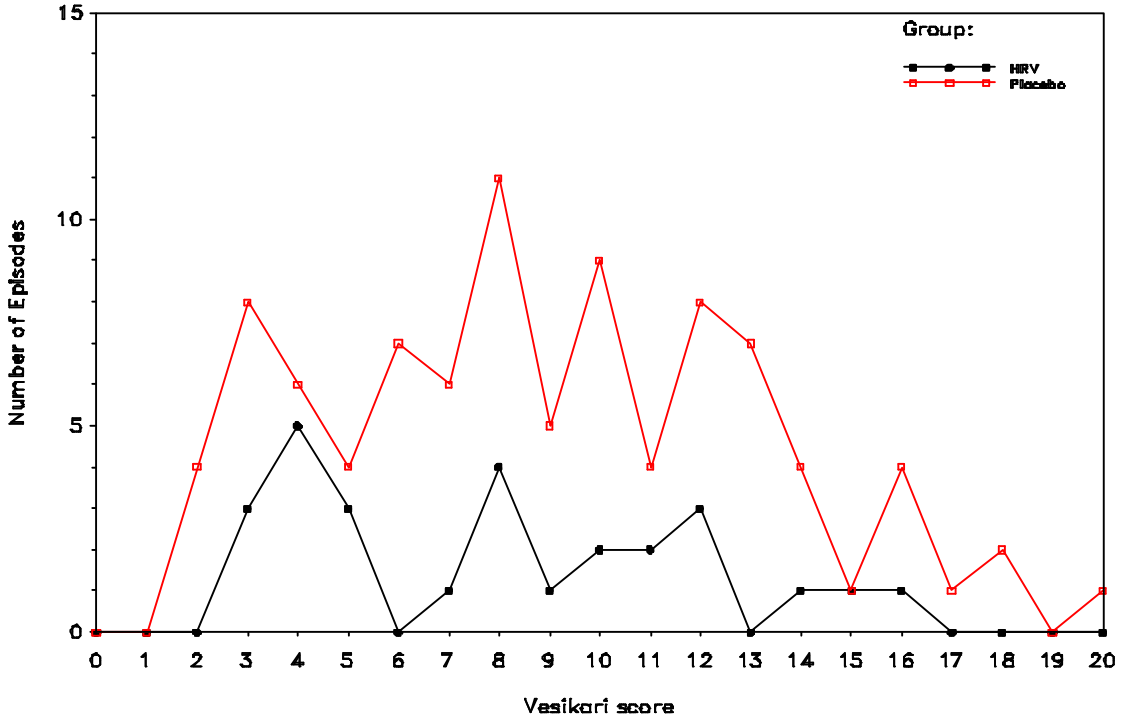
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 94 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1575 | 238 | 15.1 | 13.4 | 17.0 | 4.9 | -14.0 | 20.7 | 0.609 |
| Placebo | 1573 | 250 | 15.9 | 14.1 | 17.8 | - | - | - | - |

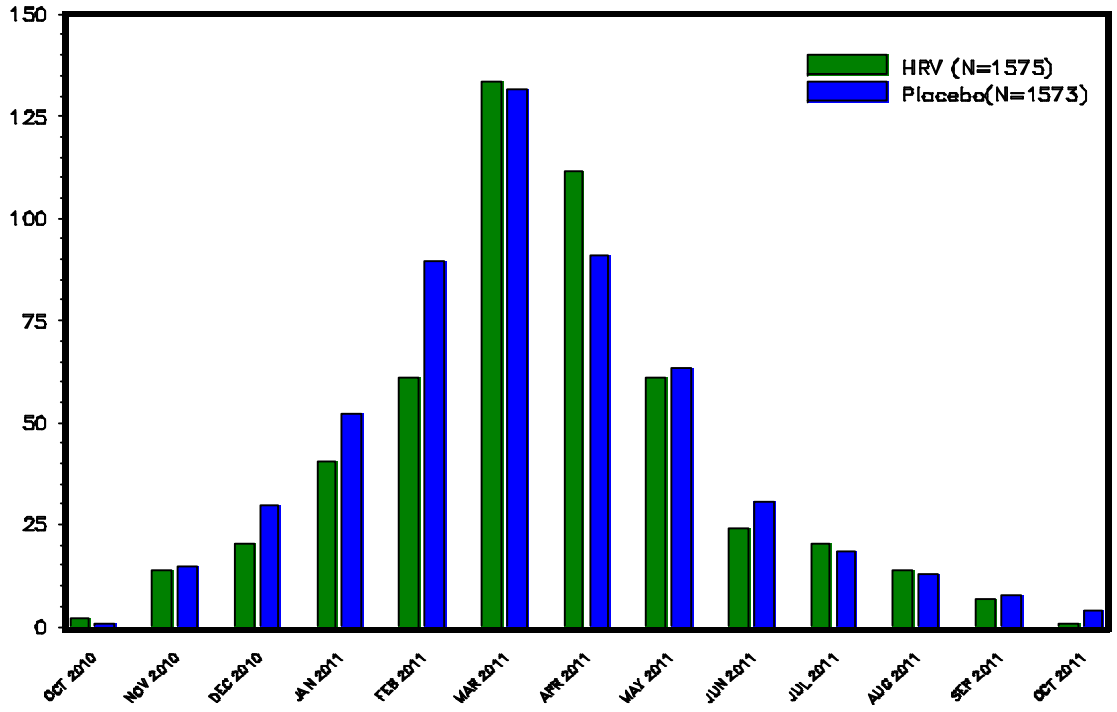
HRV = HRV
Placebo = Placebo
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 11 Distribution of Vesikari score for RV GE episodes reported from 2 weeks after dose 2 up to Visit 6 (ATP cohort for efficacy)**



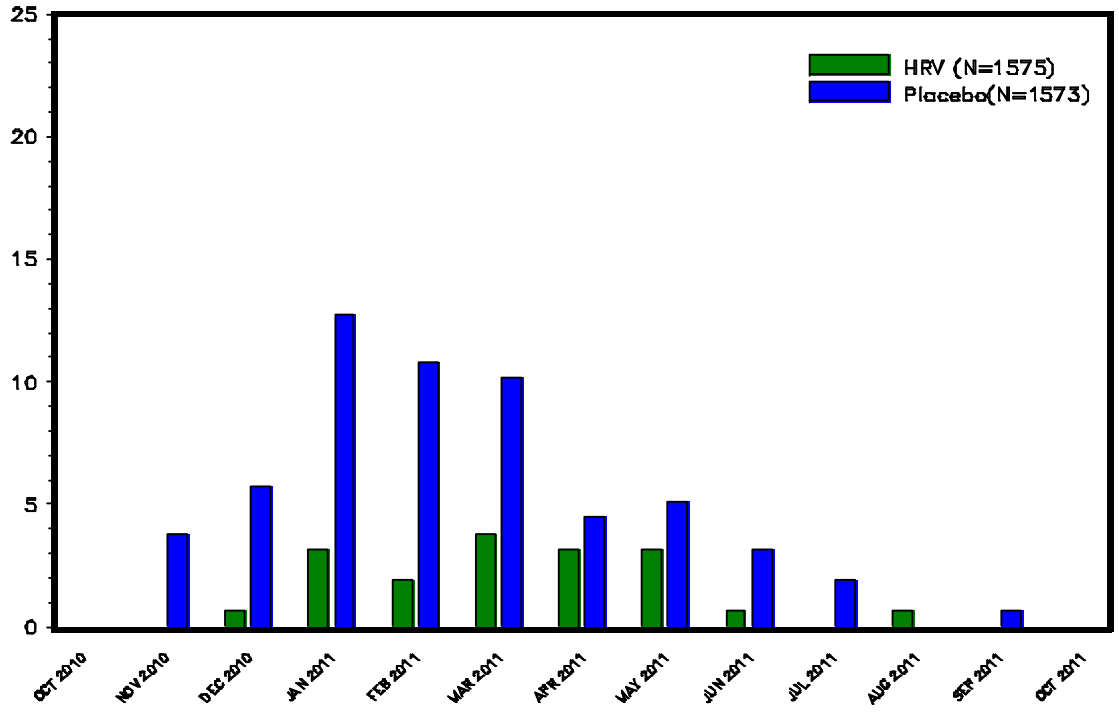

X axis = Score for each episodes computed based on the vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 12** **Seasonal distribution of GE episodes reported from 2 weeks after Dose 2 up to Visit 6 for HRV group and placebo group (ATP cohort for efficacy)**



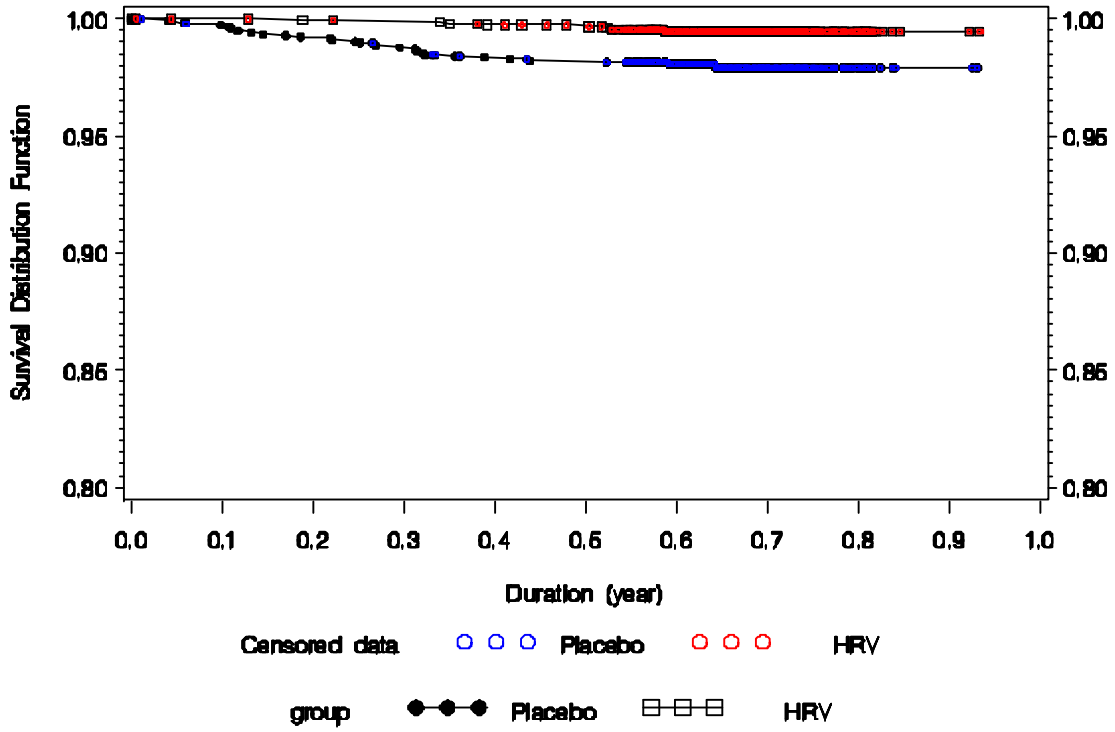

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 13** **Seasonal distribution of RVGE episodes reported from 2 weeks after Dose 2 up to Visit 6 for HRV group and placebo group (ATP cohort for efficacy)**



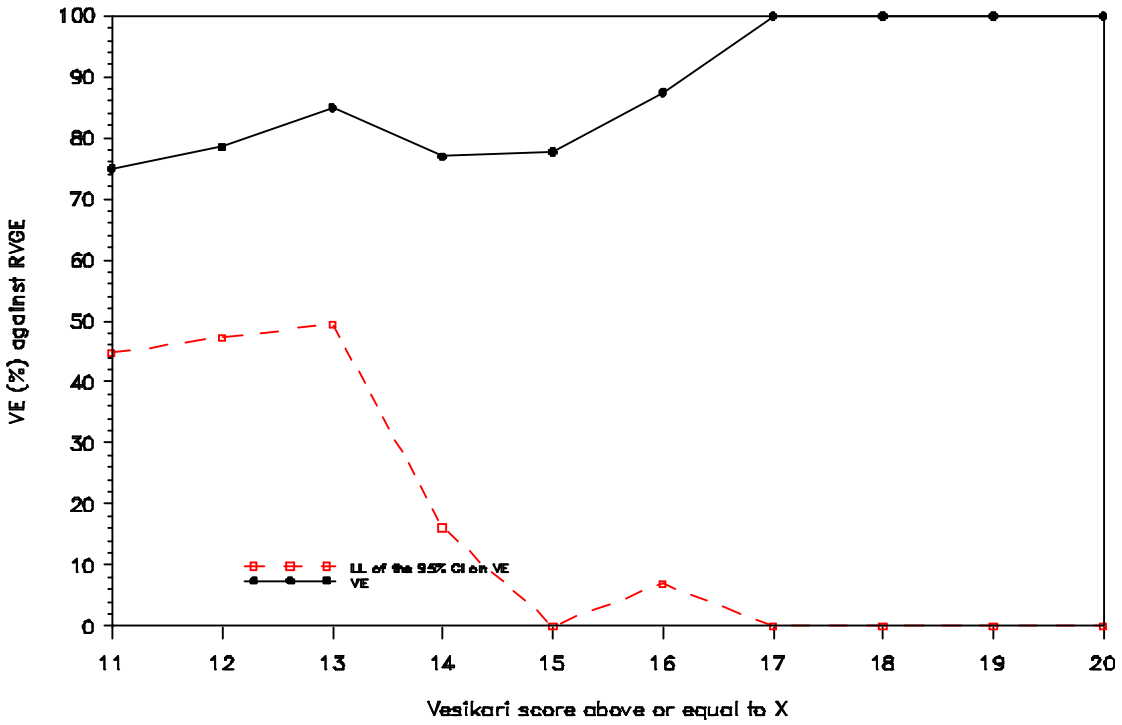

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N= Number of subjects included in each group

**Figure 14 The Kaplan Meier curve for severe RV GE from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



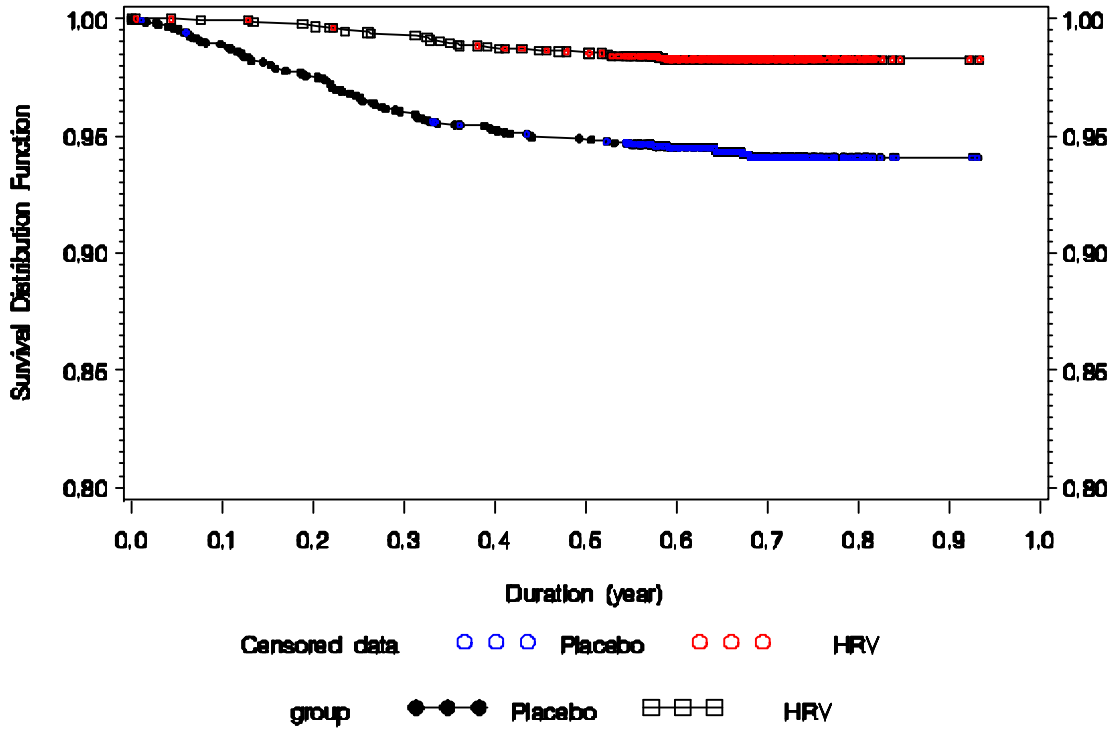

Y-axis has been cut at 0.8

**Figure 15 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from 2 weeks post dose 2 to visit 6 (ATP cohort for efficacy)**



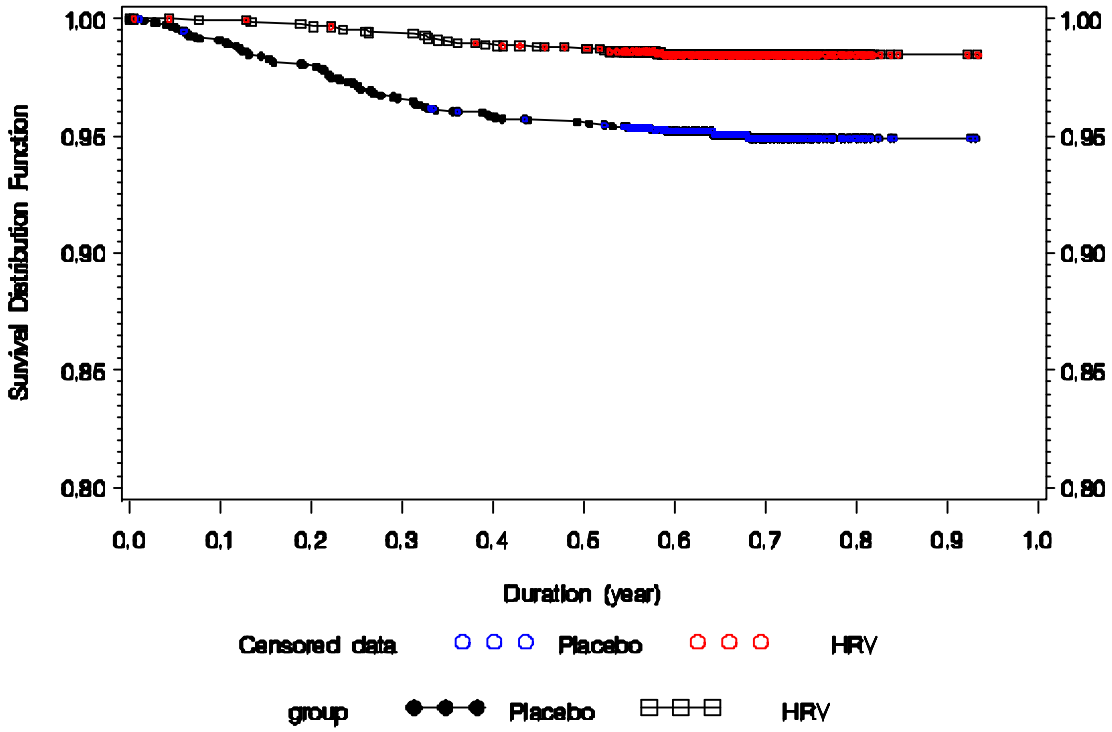

Y-axis has been cut at 0
X-axis is cut at 11
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 16 The Kaplan Meier curve for any RV GE from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



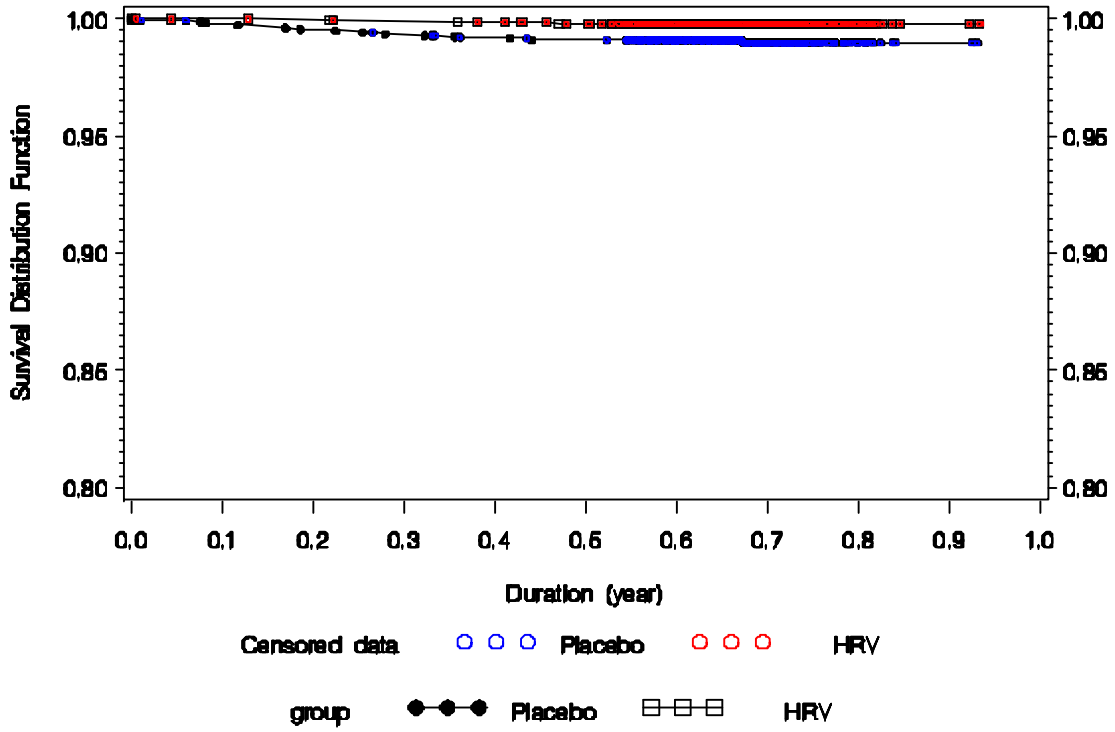

Y-axis has been cut at 0.8

**Figure 17 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



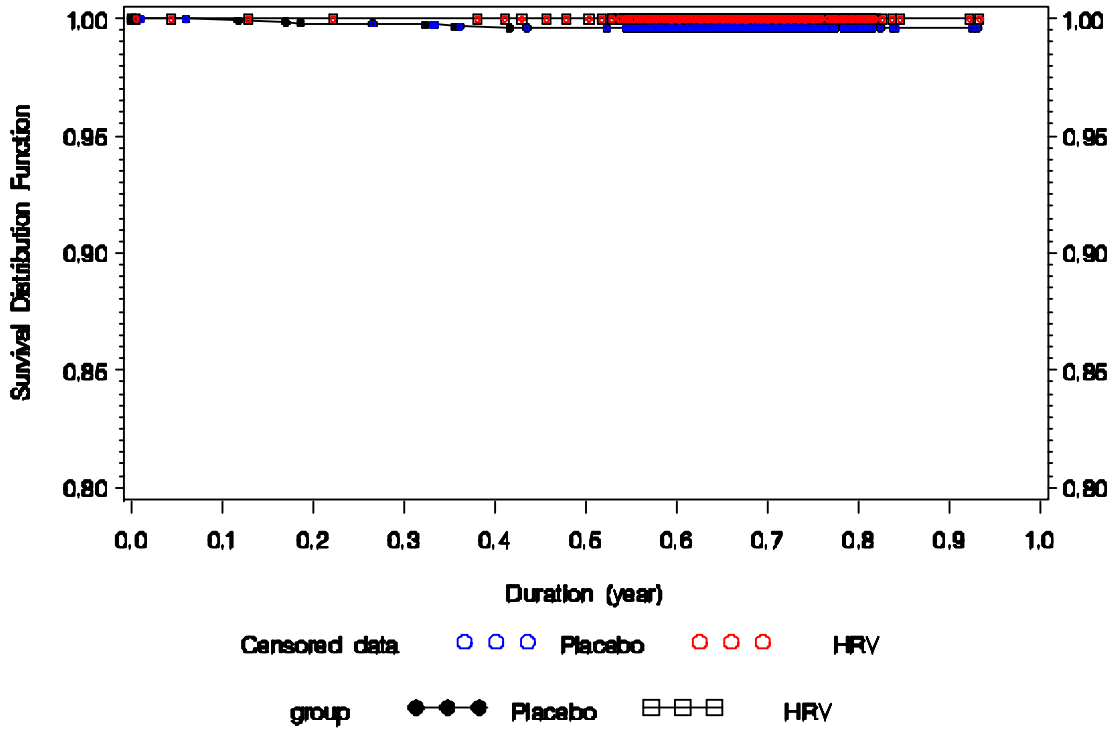

Y-axis has been cut at 0.8

**Figure 18 The Kaplan Meier curve for any RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**



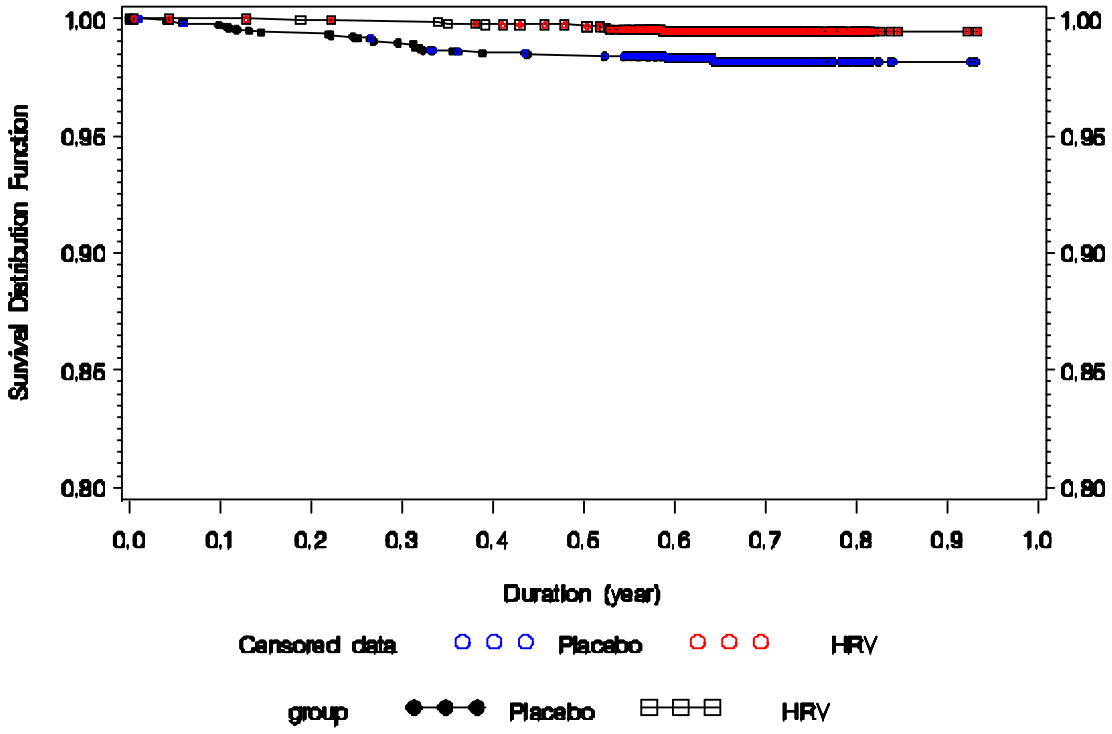

Y-axis has been cut at 0.8

**Figure 19 The Kaplan Meier curve for severe RV GE due to G1 wild type from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

**Figure 20** **The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from 2 weeks after Dose 2 up to Visit 6 (ATP cohort for efficacy)**




Y-axis has been cut at 0.8

## 11.4.3. Characterization of GE episodes after Visit 6 up to Visit 7

### Table 95 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

| | | HRV N = 1500 | | Placebo N = 1479 | | Total N = 2979 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 1212 | 80.8 | 1171 | 79.2 | 2383 | 80.0 |
| | 1 | 242 | 16.1 | 252 | 17.0 | 494 | 16.6 |
| | 2 | 28 | 1.9 | 46 | 3.1 | 74 | 2.5 |
| | 3 | 13 | 0.9 | 6 | 0.4 | 19 | 0.6 |
| | 4 | 1 | 0.1 | 3 | 0.2 | 4 | 0.1 |
| | 5 | 2 | 0.1 | 1 | 0.1 | 3 | 0.1 |
| | 6 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | 8 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 288 | 19.2 | 308 | 20.8 | 596 | 20.0 |
| RVGE | 0 | 1457 | 97.1 | 1401 | 94.7 | 2858 | 95.9 |
| | 1 | 43 | 2.9 | 78 | 5.3 | 121 | 4.1 |
| | Any | 43 | 2.9 | 78 | 5.3 | 121 | 4.1 |
| Severe GE | 0 | 1428 | 95.2 | 1376 | 93.0 | 2804 | 94.1 |
| | 1 | 66 | 4.4 | 97 | 6.6 | 163 | 5.5 |
| | 2 | 3 | 0.2 | 4 | 0.3 | 7 | 0.2 |
| | 3 | 2 | 0.1 | 2 | 0.1 | 4 | 0.1 |
| | 4 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 72 | 4.8 | 103 | 7.0 | 175 | 5.9 |
| Severe RVGE | 0 | 1487 | 99.1 | 1436 | 97.1 | 2923 | 98.1 |
| | 1 | 13 | 0.9 | 43 | 2.9 | 56 | 1.9 |
| | Any | 13 | 0.9 | 43 | 2.9 | 56 | 1.9 |

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

### Table 96 Number of GE episodes reported from Visit 6 up to Visit 7 by severity using the 20-point Vesikari scale (ATP cohort for efficacy - second year follow-up period)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| **Event** | **Severity using 20 point Vesikari scale** | **n** | **%** | **n** | **%** |
| GE | Mild (1-6) | 163 | 44.7 | 155 | 40.9 |
| | Moderate (7-10) | 120 | 32.9 | 113 | 29.8 |
| | Severe (≥11) | 82 | 22.5 | 111 | 29.3 |
| | Any | 365 | 100 | 379 | 100 |
| RVGE | Mild (1-6) | 17 | 39.5 | 16 | 20.5 |
| | Moderate (7-10) | 13 | 30.2 | 19 | 24.4 |
| | Severe (≥11) | 13 | 30.2 | 43 | 55.1 |
| | Any | 43 | 100 | 78 | 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

## Table 97 Percentage of GE episodes with no available stool results from Visit 6 up to Visit 7 (ATP cohort for efficacy – second year follow-up period)

| | HRV N' = 365 | | Placebo N' = 379 | | Total N' = 744 | |
|---|---|---|---|---|---|---|
| **Categories** | **n** | **%** | **n** | **%** | **n** | **%** |
| No stool results available | 10 | 2.7 | 19 | 5.0 | 29 | 3.9 |
| no stools collected* | 8 | 2.2 | 18 | 4.7 | 26 | 3.5 |
| stools collected but no results available | 2 | 0.5 | 1 | 0.3 | 3 | 0.4 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category
*There is one episode of GE for which sample was collected but was not sent to lab. Hence the sample was not tested.

## Table 98 Percentage of subjects with RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

| | HRV N = 1500 | | Placebo N = 1479 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 43 | 2.9 | 78 | 5.3 |
| G1 WT | 19 | 1.3 | 31 | 2.1 |
| G2 | 20 | 1.3 | 37 | 2.5 |
| G3 | 1 | 0.1 | 4 | 0.3 |
| G9 | 1 | 0.1 | 4 | 0.3 |
| GX | 4 | 0.3 | 6 | 0.4 |
| P4 | 21 | 1.4 | 40 | 2.7 |
| P8 WT | 22 | 1.5 | 37 | 2.5 |
| P9 | 0 | 0.0 | 1 | 0.1 |
| PX | 1 | 0.1 | 0 | 0.0 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 99 Percentage of subjects with severe RV GE episodes from Visit 6 up to Visit 7 by G and P type (ATP cohort for efficacy - second year follow-up period)

| | HRV N = 1500 | | Placebo N = 1479 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 13 | 0.9 | 43 | 2.9 |
| G1 WT | 9 | 0.6 | 19 | 1.3 |
| G2 | 4 | 0.3 | 16 | 1.1 |
| G3 | 0 | 0.0 | 1 | 0.1 |
| G9 | 0 | 0.0 | 3 | 0.2 |
| GX | 0 | 0.0 | 6 | 0.4 |
| P4 | 5 | 0.3 | 18 | 1.2 |
| P8 WT | 8 | 0.5 | 24 | 1.6 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 100 Number of RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

| Serotype | HRV N'=43 | | Placebo N'=78 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 1.28 |
| G1WT+G2+P4+P8WT | 1 | 2.33 | 1 | 1.28 |
| G1WT+G2+P8WT | 0 | 0.00 | 2 | 2.56 |
| G1WT+P4 | 1 | 2.33 | 5 | 6.41 |
| G1WT+P8WT | 17 | 39.53 | 22 | 28.21 |
| G2+G3+P4 | 1 | 2.33 | 0 | 0.00 |
| G2+P4 | 18 | 41.86 | 33 | 42.31 |
| G3+P8WT | 0 | 0.00 | 3 | 3.85 |
| G3+P9 | 0 | 0.00 | 1 | 1.28 |
| G9+P8WT | 1 | 2.33 | 4 | 5.13 |
| GX | 0 | 0.00 | 1 | 1.28 |
| GX+P8WT | 3 | 6.98 | 5 | 6.41 |
| GX+PX | 1 | 2.33 | 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 Visit 6 up to Visit 7
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 101 Number of severe RV GE episodes reported from Visit 6 up to Visit 7, by G and P type (ATP cohort for efficacy - second year follow-up period)

| Serotype | HRV N'=13 | | Placebo N'=43 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 2.33 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 2.33 |
| G1WT+P4 | 1 | 7.69 | 3 | 6.98 |
| G1WT+P8WT | 8 | 61.54 | 14 | 32.56 |
| G2+P4 | 4 | 30.77 | 14 | 32.56 |
| G3+P8WT | 0 | 0.00 | 1 | 2.33 |
| G9+P8WT | 0 | 0.00 | 3 | 6.98 |
| GX | 0 | 0.00 | 1 | 2.33 |
| GX+P8WT | 0 | 0.00 | 5 | 11.63 |

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 severe RV GE episodes reported from Visit 6 up to Visit 7
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 102 Duration (in years) of efficacy follow-up period - from Visit 6 up to Visit 7 (ATP cohort for efficacy - second year follow-up period)

| | | HRV N = 1500 | Placebo N = 1479 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 1040 | 1029 |
| | Mean | 0.69 | 0.70 |
| | Minimum | 0.40 | 0.28 |
| | Q1 | 0.59 | 0.59 |
| | Median | 0.69 | 0.70 |
| | Q3 | 0.79 | 0.79 |
| | Maximum | 0.96 | 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

## 11.4.4. Vaccine efficacy from after Visit 6 up to Visit 7

### 11.4.4.1. Vaccine efficacy against severe RV GE

**Table 103 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1500 | 13 | 0.9 | 0.5 | 1.5 | 70.2 | 43.5 | 85.3 | <0.001 |
| Placebo | 1479 | 43 | 2.9 | 2.1 | 3.9 | - | - | - | - |

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

### 11.4.4.2. Vaccine efficacy against any RV GE

**Table 104 Percentage of subjects reporting any RV GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1500 | 43 | 2.9 | 2.1 | 3.8 | 45.6 | 20.1 | 63.4 | 0.001 |
| Placebo | 1479 | 78 | 5.3 | 4.2 | 6.5 | - | - | - | - |

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

### 11.4.4.3. Vaccine efficacy against circulating RV types

**Table 105 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1500 | 9 | 0.6 | 0.3 | 1.1 | 53.3 | -8.3 | 81.4 | 0.080 |
| | Placebo | 1479 | 19 | 1.3 | 0.8 | 2.0 | - | - | - | - |
| G2 | HRV | 1500 | 4 | 0.3 | 0.1 | 0.7 | 75.4 | 23.6 | 94.0 | 0.011 |
| | Placebo | 1479 | 16 | 1.1 | 0.6 | 1.8 | - | - | - | - |
| G3 | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3745.4 | 100.0 | 0.993 |
| | Placebo | 1479 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| G9 | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -138.6 | 100.0 | 0.245 |
| | Placebo | 1479 | 3 | 0.2 | 0.0 | 0.6 | - | - | - | - |
| GX | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 16.3 | 100.0 | 0.030 |
| | Placebo | 1479 | 6 | 0.4 | 0.1 | 0.9 | - | - | - | - |
| P4 | HRV | 1500 | 5 | 0.3 | 0.1 | 0.8 | 72.6 | 23.5 | 92.1 | 0.010 |
| | Placebo | 1479 | 18 | 1.2 | 0.7 | 1.9 | - | - | - | - |
| P8 WT | HRV | 1500 | 8 | 0.5 | 0.2 | 1.0 | 67.1 | 24.4 | 87.2 | 0.006 |
| | Placebo | 1479 | 24 | 1.6 | 1.0 | 2.4 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1500 | 4 | 0.3 | 0.1 | 0.7 | 84.8 | 56.3 | 96.2 | <0.001 |
| | Placebo | 1479 | 26 | 1.8 | 1.2 | 2.6 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 106 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Visit 6 up to Visit 7 by RV type (ATP cohort for efficacy for second year follow up)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1500 | 19 | 1.3 | 0.8 | 2.0 | 39.6 | -10.4 | 67.7 | 0.108 |
| | Placebo | 1479 | 31 | 2.1 | 1.4 | 3.0 | - | - | - | - |
| G2 | HRV | 1500 | 20 | 1.3 | 0.8 | 2.1 | 46.7 | 5.8 | 70.7 | 0.029 |
| | Placebo | 1479 | 37 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| G3 | HRV | 1500 | 1 | 0.1 | 0.0 | 0.4 | 75.4 | -149.1 | 99.5 | 0.366 |
| | Placebo | 1479 | 4 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G9 | HRV | 1500 | 1 | 0.1 | 0.0 | 0.4 | 75.4 | -149.1 | 99.5 | 0.366 |
| | Placebo | 1479 | 4 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| GX | HRV | 1500 | 4 | 0.3 | 0.1 | 0.7 | 34.3 | -177.2 | 86.4 | 0.737 |
| | Placebo | 1479 | 6 | 0.4 | 0.1 | 0.9 | - | - | - | - |
| P4 | HRV | 1500 | 21 | 1.4 | 0.9 | 2.1 | 48.2 | 10.1 | 71.0 | 0.018 |
| | Placebo | 1479 | 40 | 2.7 | 1.9 | 3.7 | - | - | - | - |
| P8 WT | HRV | 1500 | 22 | 1.5 | 0.9 | 2.2 | 41.4 | -2.0 | 67.1 | 0.060 |
| | Placebo | 1479 | 37 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| P9 | HRV | 1500 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3745.4 | 100.0 | 0.993 |
| | Placebo | 1479 | 1 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| PX | HRV | 1500 | 1 | 0.1 | 0.0 | 0.4 | Und. | Und. | Und. | 1.000 |
| | Placebo | 1479 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1500 | 25 | 1.7 | 1.1 | 2.5 | 51.7 | 20.5 | 71.3 | 0.003 |
| | Placebo | 1479 | 51 | 3.4 | 2.6 | 4.5 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain
Und. = cannot be estimated

### 11.4.4.4. Vaccine efficacy against hospitalisation due to RV

**Table 107 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 2 | 0.1 | 0.0 | 0.5 | 71.8 | -48.0 | 97.1 | 0.173 |
| Placebo | 1479 | 7 | 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
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

### 11.4.4.5. Vaccine efficacy against all cause GE

**Table 108 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 288 | 19.2 | 17.2 | 21.3 | 7.8 | -8.6 | 21.8 | 0.342 |
| Placebo | 1479 | 308 | 20.8 | 18.8 | 23.0 | - | - | - | - |

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

**Table 109 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 72 | 4.8 | 3.8 | 6.0 | 31.1 | 6.0 | 49.7 | 0.018 |
| Placebo | 1479 | 103 | 7.0 | 5.7 | 8.4 | - | - | - | - |

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

**Table 110 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine Visit 6 up to Visit 7 (ATP cohort for efficacy for second year follow up)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1500 | 6 | 0.4 | 0.1 | 0.9 | 78.9 | 48.0 | 92.8 | <0.001 |
| Placebo | 1479 | 28 | 1.9 | 1.3 | 2.7 | - | - | - | - |

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

# 11.5. Total vaccinated cohort analysis

## 11.5.1. Characterization of GE episodes from Dose 1 to Visit 7

### Table 111 Percentage of subjects with vaccine virus in stool samples collected in case of GE episode from Dose 1 up to Visit 7 (Total vaccinated cohort)

| Group | N | n | % | 95%CI | |
|---|---|---|---|---|---|
| | | | | LL | UL |
| **HRV** | 1666 | 2 | 0.1 | 0.0 | 0.4 |
| **Placebo** | 1667 | 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

### Table 112 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 817 | 49.0 | 800 | 48.0 | 1617 | 48.5 |
| | 1 | 508 | 30.5 | 496 | 29.8 | 1004 | 30.1 |
| | 2 | 205 | 12.3 | 229 | 13.7 | 434 | 13.0 |
| | 3 | 83 | 5.0 | 79 | 4.7 | 162 | 4.9 |
| | 4 | 25 | 1.5 | 35 | 2.1 | 60 | 1.8 |
| | 5 | 14 | 0.8 | 12 | 0.7 | 26 | 0.8 |
| | 6 | 9 | 0.5 | 8 | 0.5 | 17 | 0.5 |
| | 7 | 2 | 0.1 | 3 | 0.2 | 5 | 0.2 |
| | 8 | 0 | 0.0 | 2 | 0.1 | 2 | 0.1 |
| | 9 | 3 | 0.2 | 1 | 0.1 | 4 | 0.1 |
| | 10 | 0 | 0.0 | 2 | 0.1 | 2 | 0.1 |
| | Any | 849 | 51.0 | 867 | 52.0 | 1716 | 51.5 |
| RVGE | 0 | 1591 | 95.5 | 1491 | 89.4 | 3082 | 92.5 |
| | 1 | 75 | 4.5 | 172 | 10.3 | 247 | 7.4 |
| | 2 | 0 | 0.0 | 4 | 0.2 | 4 | 0.1 |
| | Any | 75 | 4.5 | 176 | 10.6 | 251 | 7.5 |
| Severe GE | 0 | 1456 | 87.4 | 1427 | 85.6 | 2883 | 86.5 |
| | 1 | 192 | 11.5 | 203 | 12.2 | 395 | 11.9 |
| | 2 | 10 | 0.6 | 31 | 1.9 | 41 | 1.2 |
| | 3 | 5 | 0.3 | 6 | 0.4 | 11 | 0.3 |
| | 4 | 2 | 0.1 | 0 | 0.0 | 2 | 0.1 |
| | 5 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 210 | 12.6 | 240 | 14.4 | 450 | 13.5 |
| Severe RVGE | 0 | 1641 | 98.5 | 1591 | 95.4 | 3232 | 97.0 |
| | 1 | 25 | 1.5 | 76 | 4.6 | 101 | 3.0 |
| | Any | 25 | 1.5 | 76 | 4.6 | 101 | 3.0 |

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

## Table 113 Number of GE episodes reported from Dose 1 up to Visit 7 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 778 | 54.3 | 812 | 54.0 |
| | Moderate (7-10) | 405 | 28.3 | 403 | 26.8 |
| | Severe (≥11) | 240 | 16.8 | 283 | 18.8 |
| | Unknown | 9 | 0.6 | 7 | 0.5 |
| | Any | 1423 | 99.4 | 1498 | 99.5 |
| RVGE | Mild (1-6) | 29 | 38.7 | 49 | 27.2 |
| | Moderate (7-10) | 21 | 28.0 | 55 | 30.6 |
| | Severe (≥11) | 25 | 33.3 | 76 | 42.2 |
| | Any | 75 | 100 | 180 | 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

## Table 114 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | HRV N' = 1432 | | Placebo N' = 1505 | | Total N' = 2937 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 171 | 11.9 | 165 | 11.0 | 336 | 11.4 |
| no stools collected* | 169 | 11.8 | 164 | 10.9 | 333 | 11.3 |
| stools collected but no results available | 2 | 0.1 | 1 | 0.1 | 3 | 0.1 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category
*There is one episode of GE for which sample was collected but was not sent to lab. Hence the sample was not tested.

## Table 115 Percentage of subjects with RV GE episodes from Dose 1 up to Visit 7 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| Serotype | n | % | n | % |
| Any | 75 | 4.5 | 176 | 10.6 |
| G1 WT | 22 | 1.3 | 51 | 3.1 |
| G2 | 46 | 2.8 | 110 | 6.6 |
| G3 | 2 | 0.1 | 12 | 0.7 |
| G9 | 1 | 0.1 | 5 | 0.3 |
| GX | 6 | 0.4 | 8 | 0.5 |
| P4 | 47 | 2.8 | 113 | 6.8 |
| P8 WT | 26 | 1.6 | 63 | 3.8 |
| P9 | 0 | 0.0 | 1 | 0.1 |
| PX | 4 | 0.2 | 1 | 0.1 |

WT=Wild Type
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=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 116 Percentage of subjects with severe RV GE episodes from Dose 1 up to Visit 7 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Serotype** | **n** | **%** | **n** | **%** |
| Any | 25 | 1.5 | 76 | 4.6 |
| G1 WT | 9 | 0.5 | 25 | 1.5 |
| G2 | 14 | 0.8 | 44 | 2.6 |
| G3 | 1 | 0.1 | 3 | 0.2 |
| G9 | 0 | 0.0 | 3 | 0.2 |
| GX | 1 | 0.1 | 6 | 0.4 |
| P4 | 15 | 0.9 | 44 | 2.6 |
| P8 WT | 10 | 0.6 | 31 | 1.9 |
| PX | 1 | 0.1 | 1 | 0.1 |

WT=Wild Type
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=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 117 Number of RV GE episodes reported from Dose 1 up to Visit 7, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=75 | | Placebo N'=180 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+G2+P4 | 0 | 0.00 | 4 | 2.22 |
| G1WT+G2+P4+P8WT | 1 | 1.33 | 1 | 0.56 |
| G1WT+G2+P8WT | 0 | 0.00 | 3 | 1.67 |
| G1WT+P4 | 1 | 1.33 | 6 | 3.33 |
| G1WT+P8WT | 19 | 25.33 | 38 | 21.11 |
| G1WT+PX | 1 | 1.33 | 0 | 0.00 |
| G2+G3+P4 | 1 | 1.33 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 0.56 |
| G2+P4 | 43 | 57.33 | 102 | 56.67 |
| G2+P4+P8WT | 1 | 1.33 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 0.56 |
| G3+P8WT | 1 | 1.33 | 10 | 5.56 |
| G3+P9 | 0 | 0.00 | 1 | 0.56 |
| G9+P8WT | 1 | 1.33 | 5 | 2.78 |
| GX | 0 | 0.00 | 2 | 1.11 |
| GX+P8WT | 3 | 4.00 | 6 | 3.33 |
| GX+PX | 3 | 4.00 | 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 7
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 118 Number of severe RV GE episodes reported from Dose 1 up to Visit 7, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=25 | | Placebo N,=76 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 2 | 2.63 |
| G1WT+G2+P8WT | 0 | 0.00 | 2 | 2.63 |
| G1WT+P4 | 1 | 4.00 | 3 | 3.95 |
| G1WT+P8WT | 8 | 32.00 | 18 | 23.68 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.32 |
| G2+P4 | 13 | 52.00 | 38 | 50.00 |
| G2+P4+P8WT | 1 | 4.00 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.32 |
| G3+P8WT | 1 | 4.00 | 2 | 2.63 |
| G9+P8WT | 0 | 0.00 | 3 | 3.95 |
| GX | 0 | 0.00 | 1 | 1.32 |
| GX+P8WT | 0 | 0.00 | 5 | 6.58 |
| GX+PX | 1 | 4.00 | 0 | 0.00 |

WT=Wild Type
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 severe RV GE episodes reported from dose 1 of HRV vaccine or placebo up to visit 7
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 119 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | HRV N' = 75 | | Placebo N' = 180 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.2 | - | 9.9 | - |
| | SD | 3.8 | - | 4.6 | - |
| | Median | 8.0 | - | 10.0 | - |
| | Minimum | 2.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 63 | 84.0 | 109 | 60.6 |
| | 5 | 7 | 9.3 | 29 | 16.1 |
| | more than 5 days | 5 | 6.7 | 42 | 23.3 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 7 | 9.3 | 20 | 11.1 |
| | 4 to 5 | 38 | 50.7 | 77 | 42.8 |
| | more than 5 | 30 | 40.0 | 83 | 46.1 |
| Duration of vomiting (days) | 0 day | 40 | 53.3 | 68 | 37.8 |
| | 1 day | 13 | 17.3 | 47 | 26.1 |
| | 2 days | 17 | 22.7 | 31 | 17.2 |
| | more than 2 days | 5 | 6.7 | 34 | 18.9 |
| Max number of episodes of vomiting /day | 0 | 40 | 53.3 | 68 | 37.8 |
| | 1 | 8 | 10.7 | 28 | 15.6 |
| | 2 to 4 | 23 | 30.7 | 66 | 36.7 |
| | more than 4 | 4 | 5.3 | 18 | 10.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 17 | 22.7 | 45 | 25.0 |
| | 36.6 to 37.9°C | 35 | 46.7 | 78 | 43.3 |
| | 38.0 to 38.4°C | 14 | 18.7 | 18 | 10.0 |
| | more than 38.4°C | 9 | 12.0 | 39 | 21.7 |
| Treatment | none | 39 | 52.0 | 79 | 43.9 |
| | rehydration | 32 | 42.7 | 80 | 44.4 |
| | hospitalization | 4 | 5.3 | 21 | 11.7 |
| Dehydration | none | 39 | 52.0 | 79 | 43.9 |
| | 1 to 5% | 16 | 21.3 | 19 | 10.6 |
| | more than 5 % | 20 | 26.7 | 82 | 45.6 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 120 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G1WT type (Total vaccinated cohort)**

| | | HRV N' = 22 | | Placebo N' = 52 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.8 | - | 10.8 | - |
| | SD | 4.0 | - | 4.4 | - |
| | Median | 9.5 | - | 10.0 | - |
| | Minimum | 2.0 | - | 3.0 | - |
| | Maximum | 16.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 21 | 95.5 | 28 | 53.8 |
| | 5 | 1 | 4.5 | 11 | 21.2 |
| | more than 5 days | 0 | 0.0 | 13 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 2 | 9.1 | 1 | 1.9 |
| | 4 to 5 | 9 | 40.9 | 30 | 57.7 |
| | more than 5 | 11 | 50.0 | 21 | 40.4 |
| Duration of vomiting (days) | 0 day | 12 | 54.5 | 15 | 28.8 |
| | 1 day | 2 | 9.1 | 15 | 28.8 |
| | 2 days | 6 | 27.3 | 11 | 21.2 |
| | more than 2 days | 2 | 9.1 | 11 | 21.2 |
| Max number of episodes of vomiting /day | 0 | 12 | 54.5 | 15 | 28.8 |
| | 1 | 2 | 9.1 | 9 | 17.3 |
| | 2 to 4 | 7 | 31.8 | 21 | 40.4 |
| | more than 4 | 1 | 4.5 | 7 | 13.5 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 3 | 13.6 | 12 | 23.1 |
| | 36.6 to 37.9°C | 8 | 36.4 | 22 | 42.3 |
| | 38.0 to 38.4°C | 7 | 31.8 | 6 | 11.5 |
| | more than 38.4°C | 4 | 18.2 | 12 | 23.1 |
| Treatment | none | 10 | 45.5 | 18 | 34.6 |
| | rehydration | 11 | 50.0 | 26 | 50.0 |
| | hospitalization | 1 | 4.5 | 8 | 15.4 |
| Dehydration | none | 10 | 45.5 | 18 | 34.6 |
| | 1 to 5% | 5 | 22.7 | 5 | 9.6 |
| | more than 5 % | 7 | 31.8 | 29 | 55.8 |

WT = Wild Type
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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 121 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G2 type (Total vaccinated cohort)

| | | HRV N' = 46 | | Placebo N' = 112 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.1 | - | 9.4 | - |
| | SD | 3.8 | - | 4.6 | - |
| | Median | 8.0 | - | 9.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 38 | 82.6 | 70 | 62.5 |
| | 5 | 4 | 8.7 | 15 | 13.4 |
| | more than 5 days | 4 | 8.7 | 27 | 24.1 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 5 | 10.9 | 17 | 15.2 |
| | 4 to 5 | 24 | 52.2 | 42 | 37.5 |
| | more than 5 | 17 | 37.0 | 53 | 47.3 |
| Duration of vomiting (days) | 0 day | 24 | 52.2 | 45 | 40.2 |
| | 1 day | 10 | 21.7 | 31 | 27.7 |
| | 2 days | 9 | 19.6 | 18 | 16.1 |
| | more than 2 days | 3 | 6.5 | 18 | 16.1 |
| Max number of episodes of vomiting /day | 0 | 24 | 52.2 | 45 | 40.2 |
| | 1 | 5 | 10.9 | 15 | 13.4 |
| | 2 to 4 | 15 | 32.6 | 41 | 36.6 |
| | more than 4 | 2 | 4.3 | 11 | 9.8 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 13 | 28.3 | 30 | 26.8 |
| | 36.6 to 37.9°C | 21 | 45.7 | 47 | 42.0 |
| | 38.0 to 38.4°C | 8 | 17.4 | 12 | 10.7 |
| | more than 38.4°C | 4 | 8.7 | 23 | 20.5 |
| Treatment | none | 24 | 52.2 | 57 | 50.9 |
| | rehydration | 19 | 41.3 | 42 | 37.5 |
| | hospitalization | 3 | 6.5 | 13 | 11.6 |
| Dehydration | none | 24 | 52.2 | 57 | 50.9 |
| | 1 to 5% | 9 | 19.6 | 12 | 10.7 |
| | more than 5 % | 13 | 28.3 | 43 | 38.4 |

N' = number of RV GE episodes reported in each group
n/% = number/percentage of specified symptom reported in each group among N'
Value= value of the considered parameter
SD= standard deviation
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 122 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G3 type (Total vaccinated cohort)**

| | | HRV N' = 2 | | Placebo N' = 12 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.5 | - | 8.8 | - |
| | SD | 4.9 | - | 4.3 | - |
| | Median | 7.5 | - | 8.5 | - |
| | Minimum | 4.0 | - | 2.0 | - |
| | Maximum | 11.0 | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 2 | 100 | 8 | 66.7 |
| | 5 | 0 | 0.0 | 1 | 8.3 |
| | more than 5 days | 0 | 0.0 | 3 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 50.0 | 2 | 16.7 |
| | 4 to 5 | 0 | 0.0 | 6 | 50.0 |
| | more than 5 | 1 | 50.0 | 4 | 33.3 |
| Duration of vomiting (days) | 0 day | 0 | 0.0 | 5 | 41.7 |
| | 1 day | 1 | 50.0 | 2 | 16.7 |
| | 2 days | 1 | 50.0 | 4 | 33.3 |
| | more than 2 days | 0 | 0.0 | 1 | 8.3 |
| Max number of episodes of vomiting /day | 0 | 0 | 0.0 | 5 | 41.7 |
| | 1 | 1 | 50.0 | 4 | 33.3 |
| | 2 to 4 | 1 | 50.0 | 2 | 16.7 |
| | more than 4 | 0 | 0.0 | 1 | 8.3 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 50.0 | 4 | 33.3 |
| | 36.6 to 37.9°C | 0 | 0.0 | 5 | 41.7 |
| | 38.0 to 38.4°C | 0 | 0.0 | 1 | 8.3 |
| | more than 38.4°C | 1 | 50.0 | 2 | 16.7 |
| Treatment | none | 2 | 100 | 6 | 50.0 |
| | rehydration | 0 | 0.0 | 6 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 2 | 100 | 6 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 8.3 |
| | more than 5 % | 0 | 0.0 | 5 | 41.7 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 123 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By G9 type (Total vaccinated cohort)**

| | | HRV N' = 1 | | Placebo N' = 5 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 4.0 | - | 10.6 | - |
| | SD | 0.0 | - | 4.0 | - |
| | Median | 4.0 | - | 12.0 | - |
| | Minimum | 4.0 | - | 5.0 | - |
| | Maximum | 4.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 3 | 60.0 |
| | 5 | 0 | 0.0 | 1 | 20.0 |
| | more than 5 days | 0 | 0.0 | 1 | 20.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 0 | 0.0 |
| | 4 to 5 | 1 | 100 | 3 | 60.0 |
| | more than 5 | 0 | 0.0 | 2 | 40.0 |
| Duration of vomiting (days) | 0 day | 1 | 100 | 2 | 40.0 |
| | 1 day | 0 | 0.0 | 1 | 20.0 |
| | 2 days | 0 | 0.0 | 2 | 40.0 |
| | more than 2 days | 0 | 0.0 | 0 | 0.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 100 | 2 | 40.0 |
| | 1 | 0 | 0.0 | 0 | 0.0 |
| | 2 to 4 | 0 | 0.0 | 3 | 60.0 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 0 | 0.0 |
| | 36.6 to 37.9°C | 1 | 100 | 4 | 80.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 1 | 20.0 |
| Treatment | none | 1 | 100 | 1 | 20.0 |
| | rehydration | 0 | 0.0 | 4 | 80.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 1 | 20.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 20.0 |
| | more than 5 % | 0 | 0.0 | 3 | 60.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 124 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 – By GX type (Total vaccinated cohort)

| | | HRV N' = 6 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 7.7 | - | 13.4 | - |
| | SD | 2.6 | - | 3.5 | - |
| | Median | 7.0 | - | 14.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 18.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 50.0 | 5 | 62.5 |
| | 5 | 2 | 33.3 | 2 | 25.0 |
| | more than 5 days | 1 | 16.7 | 1 | 12.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 12.5 |
| | 4 to 5 | 4 | 66.7 | 1 | 12.5 |
| | more than 5 | 2 | 33.3 | 6 | 75.0 |
| Duration of vomiting (days) | 0 day | 4 | 66.7 | 1 | 12.5 |
| | 1 day | 1 | 16.7 | 2 | 25.0 |
| | 2 days | 1 | 16.7 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 5 | 62.5 |
| Max number of episodes of vomiting /day | 0 | 4 | 66.7 | 1 | 12.5 |
| | 1 | 1 | 16.7 | 1 | 12.5 |
| | 2 to 4 | 0 | 0.0 | 4 | 50.0 |
| | more than 4 | 1 | 16.7 | 2 | 25.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 1 | 16.7 | 1 | 12.5 |
| | 36.6 to 37.9°C | 5 | 83.3 | 4 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 3 | 37.5 |
| Treatment | none | 3 | 50.0 | 1 | 12.5 |
| | rehydration | 3 | 50.0 | 6 | 75.0 |
| | hospitalization | 0 | 0.0 | 1 | 12.5 |
| Dehydration | none | 3 | 50.0 | 1 | 12.5 |
| | 1 to 5% | 2 | 33.3 | 0 | 0.0 |
| | more than 5 % | 1 | 16.7 | 7 | 87.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain

## Table 125 Characteristics of the GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | HRV N' = 1432 | | Placebo N' = 1505 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.6 | - | 7.0 | - |
| | SD | 3.7 | - | 4.0 | - |
| | Median | 6.0 | - | 6.0 | - |
| | Minimum | 0.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 15 | 1.0 | 12 | 0.8 |
| | 1 to 4 days | 1022 | 71.4 | 1024 | 68.0 |
| | 5 | 145 | 10.1 | 163 | 10.8 |
| | more than 5 days | 250 | 17.5 | 306 | 20.3 |
| Maximum number of looser than normal stools/day | 0 | 15 | 1.0 | 12 | 0.8 |
| | 1 to 3 | 255 | 17.8 | 255 | 16.9 |
| | 4 to 5 | 721 | 50.3 | 761 | 50.6 |
| | more than 5 | 441 | 30.8 | 477 | 31.7 |
| Duration of vomiting (days) | 0 day | 1021 | 71.3 | 1039 | 69.0 |
| | 1 day | 205 | 14.3 | 227 | 15.1 |
| | 2 days | 113 | 7.9 | 108 | 7.2 |
| | more than 2 days | 93 | 6.5 | 131 | 8.7 |
| Max number of episodes of vomiting /day | 0 | 1021 | 71.3 | 1039 | 69.0 |
| | 1 | 132 | 9.2 | 161 | 10.7 |
| | 2 to 4 | 241 | 16.8 | 242 | 16.1 |
| | more than 4 | 38 | 2.7 | 63 | 4.2 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 584 | 40.8 | 603 | 40.1 |
| | 36.6 to 37.9°C | 652 | 45.5 | 679 | 45.1 |
| | 38.0 to 38.4°C | 78 | 5.4 | 88 | 5.8 |
| | more than 38.4°C | 118 | 8.2 | 135 | 9.0 |
| Treatment | none | 934 | 65.2 | 962 | 63.9 |
| | rehydration | 444 | 31.0 | 444 | 29.5 |
| | hospitalization | 54 | 3.8 | 99 | 6.6 |
| Dehydration | none | 934 | 65.2 | 962 | 63.9 |
| | 1 to 5% | 208 | 14.5 | 190 | 12.6 |
| | more than 5 % | 290 | 20.3 | 353 | 23.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 126 Duration (in years) of efficacy follow-up period - from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 2351 | 2334 |
| | Mean | 1.41 | 1.40 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 1.39 | 1.38 |
| | Median | 1.50 | 1.50 |
| | Q3 | 1.59 | 1.58 |
| | Maximum | 1.68 | 1.68 |

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

## 11.5.2. Vaccine efficacy during the period from Dose 1 up to Visit 7

### 11.5.2.1. Vaccine efficacy against severe RV GE

**Table 127 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1666 | 25 | 1.5 | 1.0 | 2.2 | 67.1 | 47.7 | 79.9 | <0.001 |
| Placebo | 1667 | 76 | 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
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 128 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Severity using Vesikari scale | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| ≥11 | HRV | 1666 | 25 | 1.5 | 1.0 | 2.2 | 67.1 | 47.7 | 79.9 | <0.001 |
| | Placebo | 1667 | 76 | 4.6 | 3.6 | 5.7 | - | - | - | - |
| ≥12 | HRV | 1666 | 18 | 1.1 | 0.6 | 1.7 | 73.9 | 55.6 | 85.4 | <0.001 |
| | Placebo | 1667 | 69 | 4.1 | 3.2 | 5.2 | - | - | - | - |
| ≥13 | HRV | 1666 | 9 | 0.5 | 0.2 | 1.0 | 84.2 | 67.9 | 93.1 | <0.001 |
| | Placebo | 1667 | 57 | 3.4 | 2.6 | 4.4 | - | - | - | - |
| ≥14 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 83.0 | 63.6 | 93.0 | <0.001 |
| | Placebo | 1667 | 47 | 2.8 | 2.1 | 3.7 | - | - | - | - |
| ≥15 | HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | 89.2 | 69.9 | 97.2 | <0.001 |
| | Placebo | 1667 | 37 | 2.2 | 1.6 | 3.0 | - | - | - | - |
| ≥16 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 92.6 | 70.5 | 99.1 | <0.001 |
| | Placebo | 1667 | 27 | 1.6 | 1.1 | 2.3 | - | - | - | - |
| ≥17 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 67.2 | 100.0 | <0.001 |
| | Placebo | 1667 | 13 | 0.8 | 0.4 | 1.3 | - | - | - | - |
| ≥18 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 49.3 | 100.0 | 0.004 |
| | Placebo | 1667 | 9 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| ≥19 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -432.8 | 100.0 | 0.500 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| =20 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 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 a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P-value = Two sided Exact P-value conditional to number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.5.2.2. Vaccine efficacy against any RV GE

**Table 129 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 75 | 4.5 | 3.6 | 5.6 | 57.4 | 43.8 | 67.9 | <0.001 |
| Placebo | 1667 | 176 | 10.6 | 9.1 | 12.1 | - | - | - | - |

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

### 11.5.2.3. Vaccine efficacy against circulating RV types

**Table 130 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by RV type (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1666 | 9 | 0.5 | 0.2 | 1.0 | 64.0 | 20.2 | 85.2 | 0.009 |
| | Placebo | 1667 | 25 | 1.5 | 1.0 | 2.2 | - | - | - | - |
| G2 | HRV | 1666 | 14 | 0.8 | 0.5 | 1.4 | 68.2 | 40.8 | 83.9 | <0.001 |
| | Placebo | 1667 | 44 | 2.6 | 1.9 | 3.5 | - | - | - | - |
| G3 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 66.6 | -315.4 | 99.4 | 0.625 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| G9 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| GX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 83.3 | -37.5 | 99.6 | 0.125 |
| | Placebo | 1667 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| P4 | HRV | 1666 | 15 | 0.9 | 0.5 | 1.5 | 65.9 | 37.5 | 82.4 | <0.001 |
| | Placebo | 1667 | 44 | 2.6 | 1.9 | 3.5 | - | - | - | - |
| P8WT | HRV | 1666 | 10 | 0.6 | 0.3 | 1.1 | 67.7 | 32.4 | 85.9 | 0.001 |
| | Placebo | 1667 | 31 | 1.9 | 1.3 | 2.6 | - | - | - | - |
| PX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | -0.1 | -7754.4 | 98.7 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 16 | 1.0 | 0.5 | 1.6 | 70.9 | 48.5 | 84.4 | <0.001 |
| | Placebo | 1667 | 55 | 3.3 | 2.5 | 4.3 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
WT = Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 131 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by combination of G and P types (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT + P8WT | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 60.0 | 5.1 | 84.8 | 0.036 |
| | Placebo | 1667 | 20 | 1.2 | 0.7 | 1.8 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 80.0 | -78.8 | 99.6 | 0.219 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G2+P4 | HRV | 1666 | 14 | 0.8 | 0.5 | 1.4 | 65.8 | 36.0 | 82.8 | <0.001 |
| | Placebo | 1667 | 41 | 2.5 | 1.8 | 3.3 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 66.6 | -315.4 | 99.4 | 0.625 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| G9+P8WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |

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

## Table 132 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by RV type (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Event Type** | **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| G1WT | HRV | 1666 | 22 | 1.3 | 0.8 | 2.0 | 56.8 | 27.5 | 75.1 | <0.001 |
| | Placebo | 1667 | 51 | 3.1 | 2.3 | 4.0 | - | - | - | - |
| G2 | HRV | 1666 | 46 | 2.8 | 2.0 | 3.7 | 58.2 | 40.5 | 71.0 | <0.001 |
| | Placebo | 1667 | 110 | 6.6 | 5.5 | 7.9 | - | - | - | - |
| G3 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 83.3 | 25.1 | 98.2 | 0.013 |
| | Placebo | 1667 | 12 | 0.7 | 0.4 | 1.3 | - | - | - | - |
| G9 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 80.0 | -78.8 | 99.6 | 0.219 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| GX | HRV | 1666 | 6 | 0.4 | 0.1 | 0.8 | 25.0 | -146.6 | 78.5 | 0.791 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| P4 | HRV | 1666 | 47 | 2.8 | 2.1 | 3.7 | 58.4 | 41.0 | 71.0 | <0.001 |
| | Placebo | 1667 | 113 | 6.8 | 5.6 | 8.1 | - | - | - | - |
| P8WT | HRV | 1666 | 26 | 1.6 | 1.0 | 2.3 | 58.7 | 33.8 | 74.9 | <0.001 |
| | Placebo | 1667 | 63 | 3.8 | 2.9 | 4.8 | - | - | - | - |
| P9 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| PX | HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | -300.2 | -19610.8 | 60.4 | 0.375 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 54 | 3.2 | 2.4 | 4.2 | 59.7 | 44.3 | 71.2 | <0.001 |
| | Placebo | 1667 | 134 | 8.0 | 6.8 | 9.4 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 133 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 7 by combination of G and P types (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1666 | 20 | 1.2 | 0.7 | 1.8 | 52.4 | 17.0 | 73.5 | 0.007 |
| | Placebo | 1667 | 42 | 2.5 | 1.8 | 3.4 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 80.0 | 6.1 | 97.9 | 0.039 |
| | Placebo | 1667 | 10 | 0.6 | 0.3 | 1.1 | - | - | - | - |
| G2+P4 | HRV | 1666 | 46 | 2.8 | 2.0 | 3.7 | 57.0 | 38.7 | 70.2 | <0.001 |
| | Placebo | 1667 | 107 | 6.4 | 5.3 | 7.7 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 90.9 | 37.4 | 99.8 | 0.006 |
| | Placebo | 1667 | 11 | 0.7 | 0.3 | 1.2 | - | - | - | - |
| G9+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 80.0 | -78.8 | 99.6 | 0.219 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |

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

## Table 134 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from Dose 1 up to Visit 7 (Total vaccinated cohort)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 75 | 2306.33 | 0.033 | 0.026 | 0.041 | 0.047 | 0.034 | 0.062 |
| Placebo | 1667 | 176 | 2205.30 | 0.080 | 0.069 | 0.093 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1666 | 22 | 2342.64 | 0.009 | 0.006 | 0.014 | 0.013 | 0.006 | 0.020 |
| Placebo | 1667 | 51 | 2305.74 | 0.022 | 0.017 | 0.029 | . | . | . |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | |
| HRV | 1666 | 54 | 2314.54 | 0.023 | 0.018 | 0.030 | 0.037 | 0.025 | 0.049 |
| Placebo | 1667 | 134 | 2228.82 | 0.060 | 0.051 | 0.071 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 25 | 2336.73 | 0.011 | 0.007 | 0.016 | 0.023 | 0.014 | 0.032 |
| Placebo | 1667 | 76 | 2285.13 | 0.033 | 0.027 | 0.042 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1666 | 9 | 2348.32 | 0.004 | 0.002 | 0.007 | 0.007 | 0.002 | 0.012 |
| Placebo | 1667 | 25 | 2321.74 | 0.011 | 0.007 | 0.016 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1666 | 16 | 2339.57 | 0.007 | 0.004 | 0.011 | 0.017 | 0.010 | 0.025 |
| Placebo | 1667 | 55 | 2294.87 | 0.024 | 0.018 | 0.031 | . | . | . |

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

**Table 135 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 7 by Cox method (Total vaccinated cohort)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 75 | 2306.33 | 0.03 | 0.03 | 0.04 | 59.35 | 46.73 | 68.97 | <0.001 |
| Placebo | 1667 | 176 | 2205.30 | 0.08 | 0.07 | 0.09 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1666 | 22 | 2342.64 | 0.01 | 0.01 | 0.01 | 57.76 | 30.37 | 74.38 | <0.001 |
| Placebo | 1667 | 51 | 2305.74 | 0.02 | 0.02 | 0.03 | - | - | - | - |
| **Any RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1666 | 54 | 2314.54 | 0.02 | 0.02 | 0.03 | 61.17 | 46.74 | 71.69 | <0.001 |
| Placebo | 1667 | 134 | 2228.82 | 0.06 | 0.05 | 0.07 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 25 | 2336.73 | 0.01 | 0.01 | 0.02 | 67.99 | 49.70 | 79.63 | <0.001 |
| Placebo | 1667 | 76 | 2285.13 | 0.03 | 0.03 | 0.04 | - | - | - | - |
| **Severe RVGE of G1 WT** | | | | | | | | | | |
| HRV | 1666 | 9 | 2348.32 | 0.00 | 0.00 | 0.01 | 64.66 | 24.28 | 83.50 | 0.007 |
| Placebo | 1667 | 25 | 2321.74 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1666 | 16 | 2339.57 | 0.01 | 0.00 | 0.01 | 71.50 | 50.27 | 83.67 | <0.001 |
| Placebo | 1667 | 55 | 2294.87 | 0.02 | 0.02 | 0.03 | - | - | - | - |

WT = Wild Type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)

### 11.5.2.4. Vaccine efficacy against hospitalisation due to RV

**Table 136 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | 80.9 | 43.5 | 95.2 | <0.001 |
| Placebo | 1667 | 21 | 1.3 | 0.8 | 1.9 | - | - | - | - |

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

**Table 137 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 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 36 | 2.2 | 1.5 | 3.0 | 64.3 | 47.3 | 76.3 | <0.001 |
| Placebo | 1667 | 101 | 6.1 | 5.0 | 7.3 | - | - | - | - |

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

### 11.5.2.5. Vaccine efficacy against all cause GE

**Table 138 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 849 | 51.0 | 48.5 | 53.4 | 2.0 | -7.8 | 11.0 | 0.691 |
| Placebo | 1667 | 867 | 52.0 | 49.6 | 54.4 | - | - | - | - |

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

**Table 139 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 210 | 12.6 | 11.0 | 14.3 | 12.4 | -5.8 | 27.6 | 0.174 |
| Placebo | 1667 | 240 | 14.4 | 12.7 | 16.2 | - | - | - | - |

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

## Table 140 Percentage of subjects reporting all cause of GE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 50 | 3.0 | 2.2 | 3.9 | 45.6 | 22.4 | 62.3 | <0.001 |
| Placebo | 1667 | 92 | 5.5 | 4.5 | 6.7 | - | - | - | - |

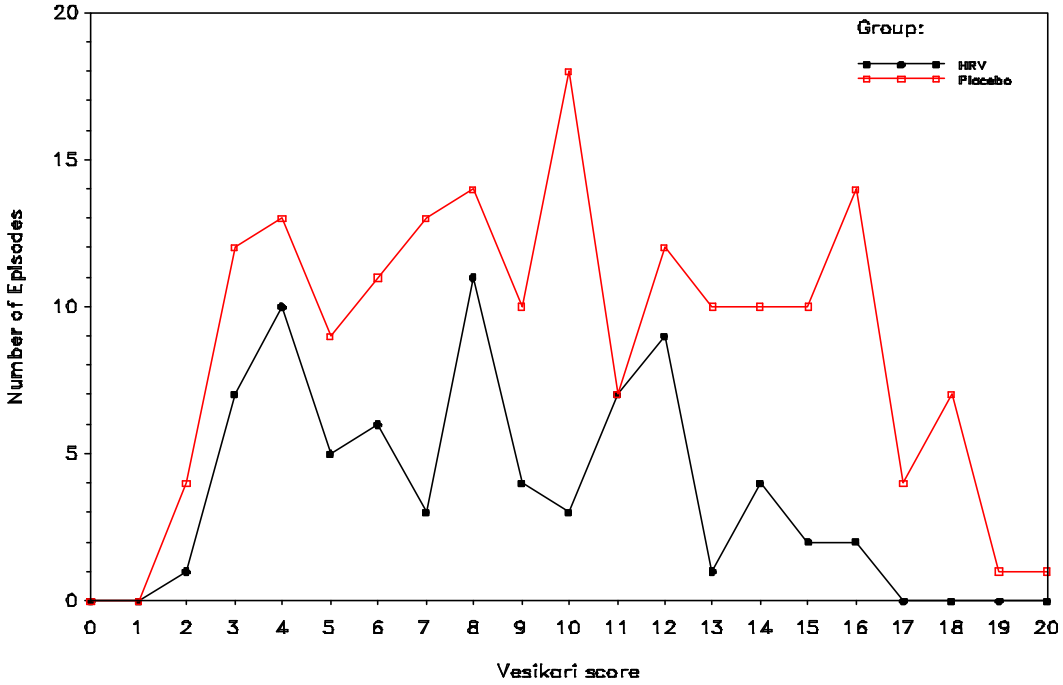
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 141 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of GE episode and efficacy of the vaccine from Dose 1 up to Visit 7 (Total vaccinated cohort)

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 378 | 22.7 | 20.7 | 24.8 | 9.1 | -4.8 | 21.1 | 0.192 |
| Placebo | 1667 | 416 | 25.0 | 22.9 | 27.1 | - | - | - | - |

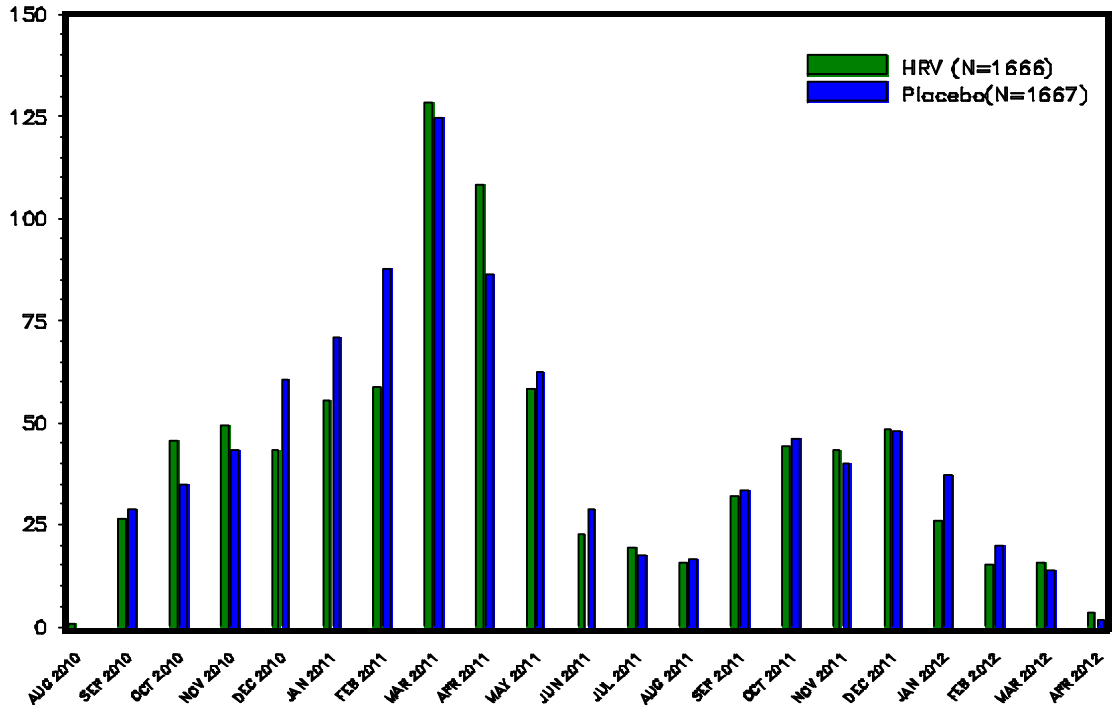
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 21 Distribution of Vesikari score for RV GE episodes reported from Dose 1 up to Visit 7 (Total vaccinated cohort)**



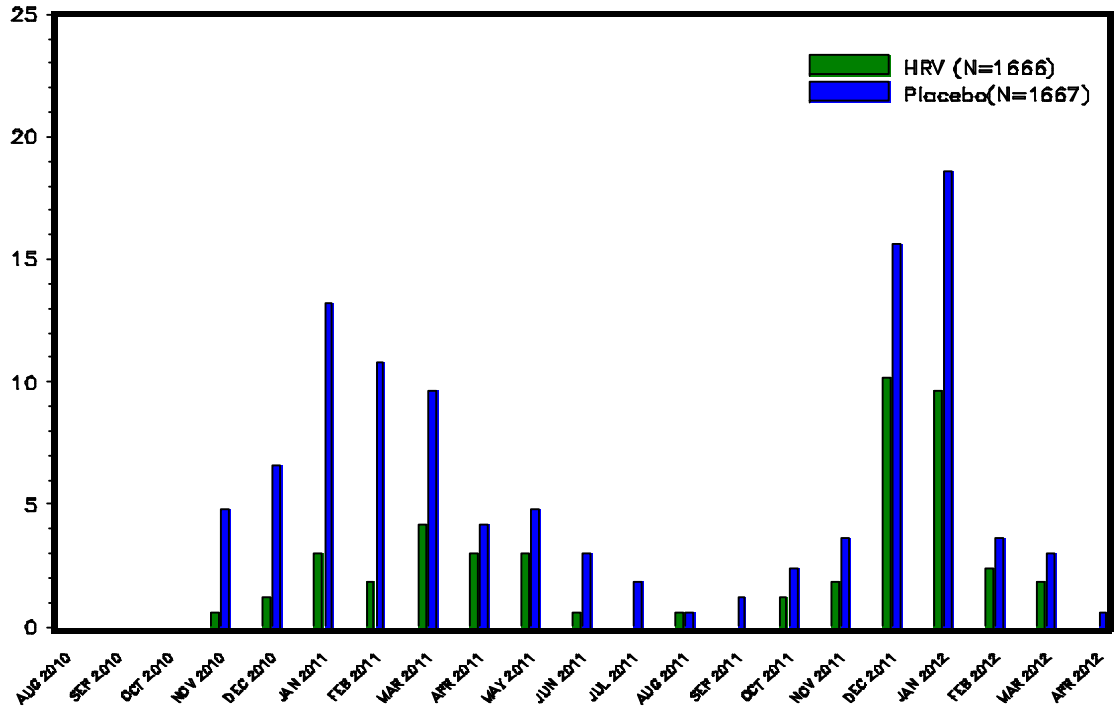

X axis = Score for each episodes computed based on the Vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 22 Seasonal distribution of GE episodes reported from Dose 1 up to Visit 7 for HRV group and placebo group (Total vaccinated cohort)**



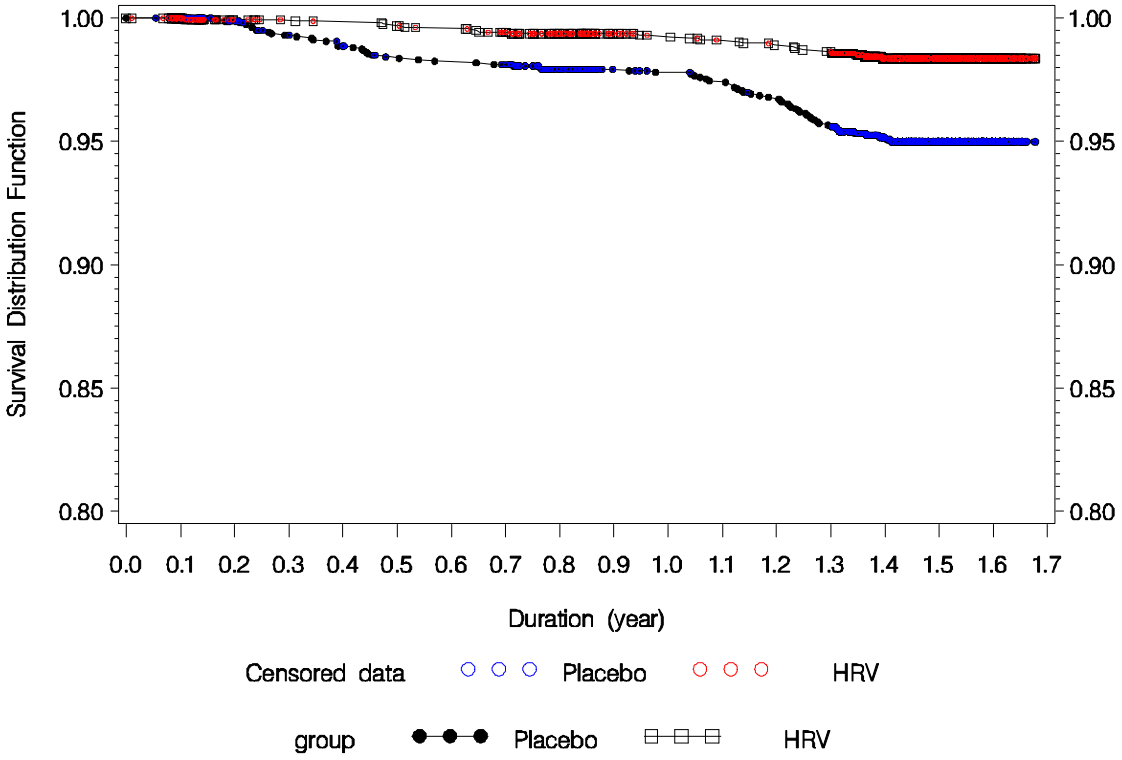

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in each group

**Figure 23 Seasonal distribution of RVGE episodes reported from Dose 1 up to Visit 7 for HRV group and placebo group (Total vaccinated cohort)**



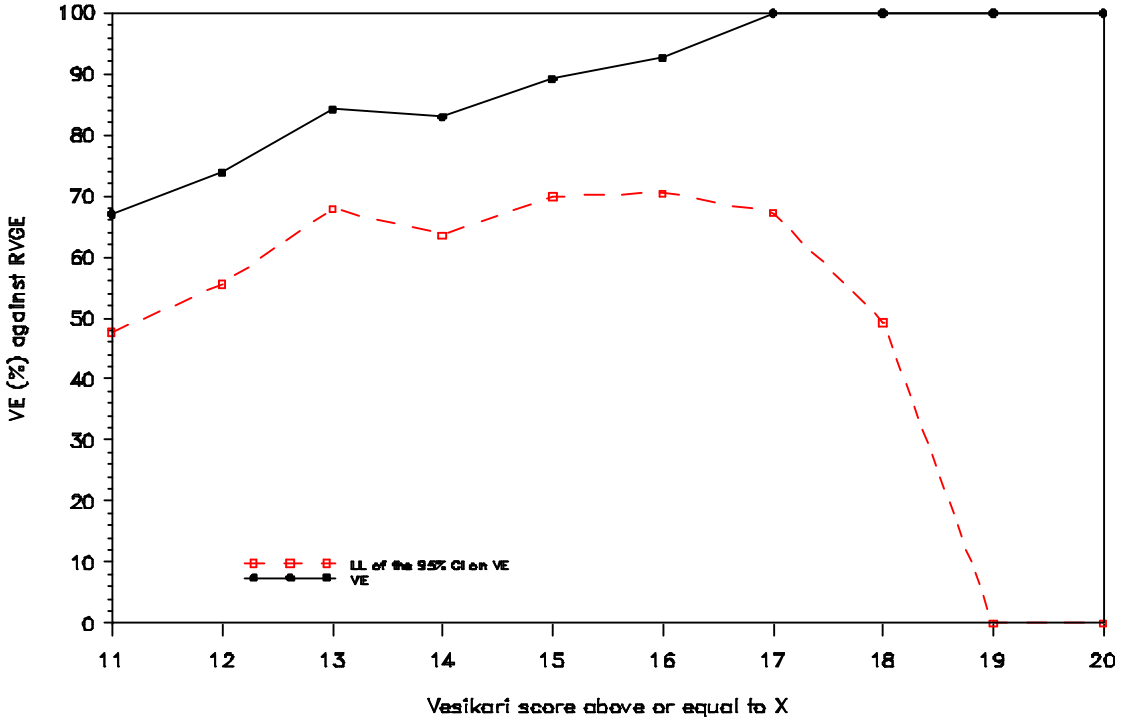

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in each group

**Figure 24 The Kaplan Meier curve for severe RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)**



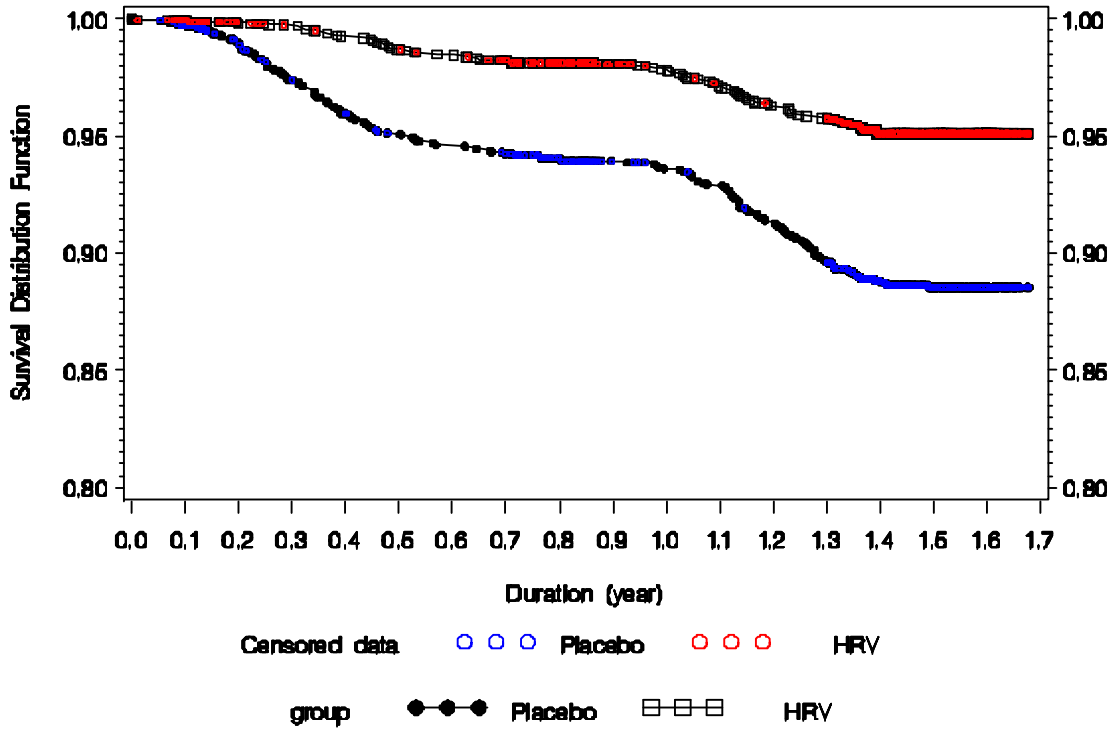

Y Axis is cut at 0.8

**Figure 25 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from Dose 1 up to Visit 7 (Total vaccinated cohort)**



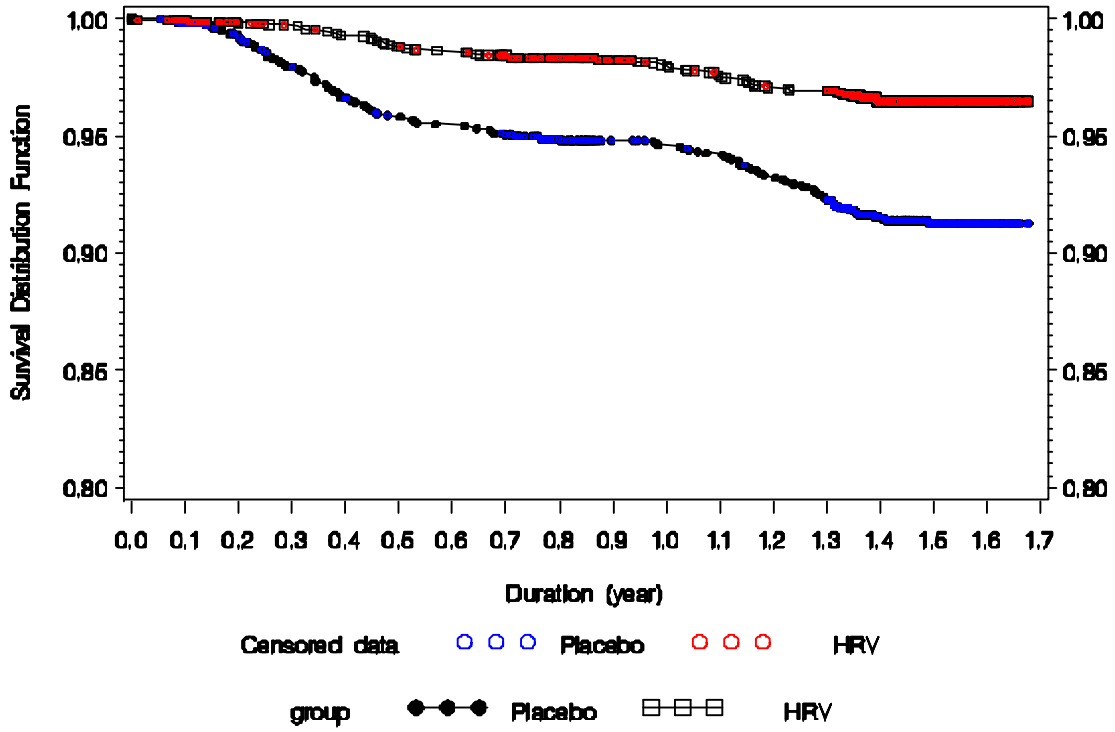

X Axis is cut at 11
Y Axis is cut at 0
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 26 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 7 (Total vaccinated cohort)**



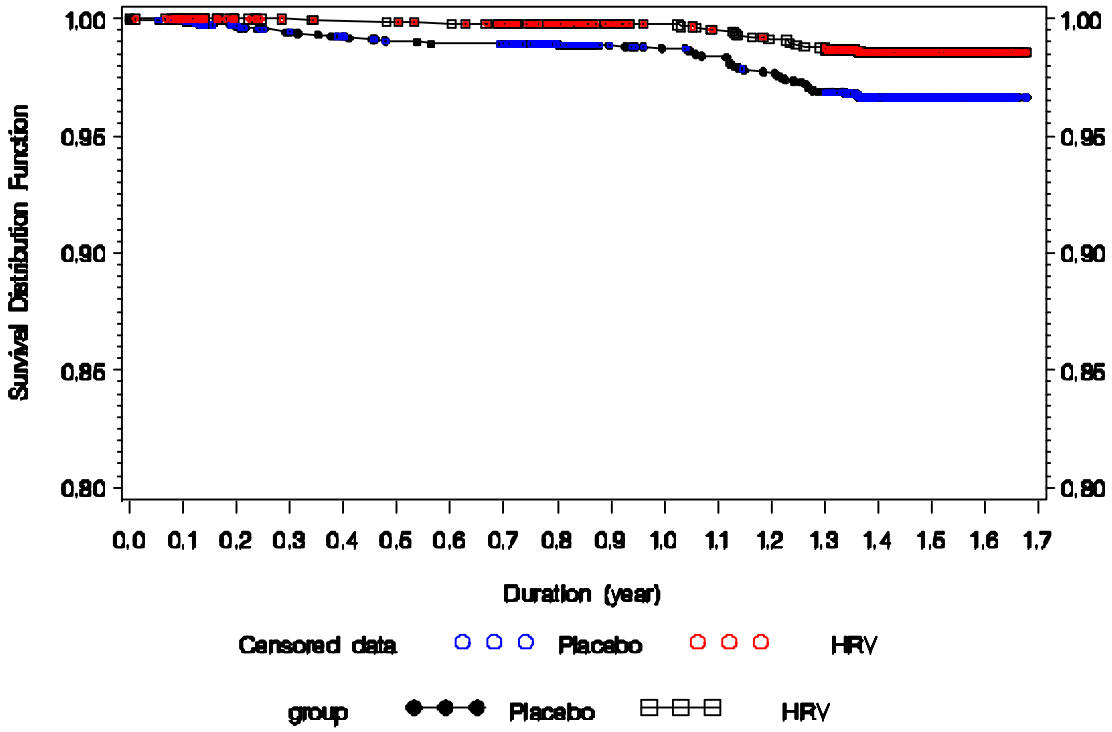

Y Axis is cut at 0.8

**Figure 27 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 7 (Total vaccinated cohort)**



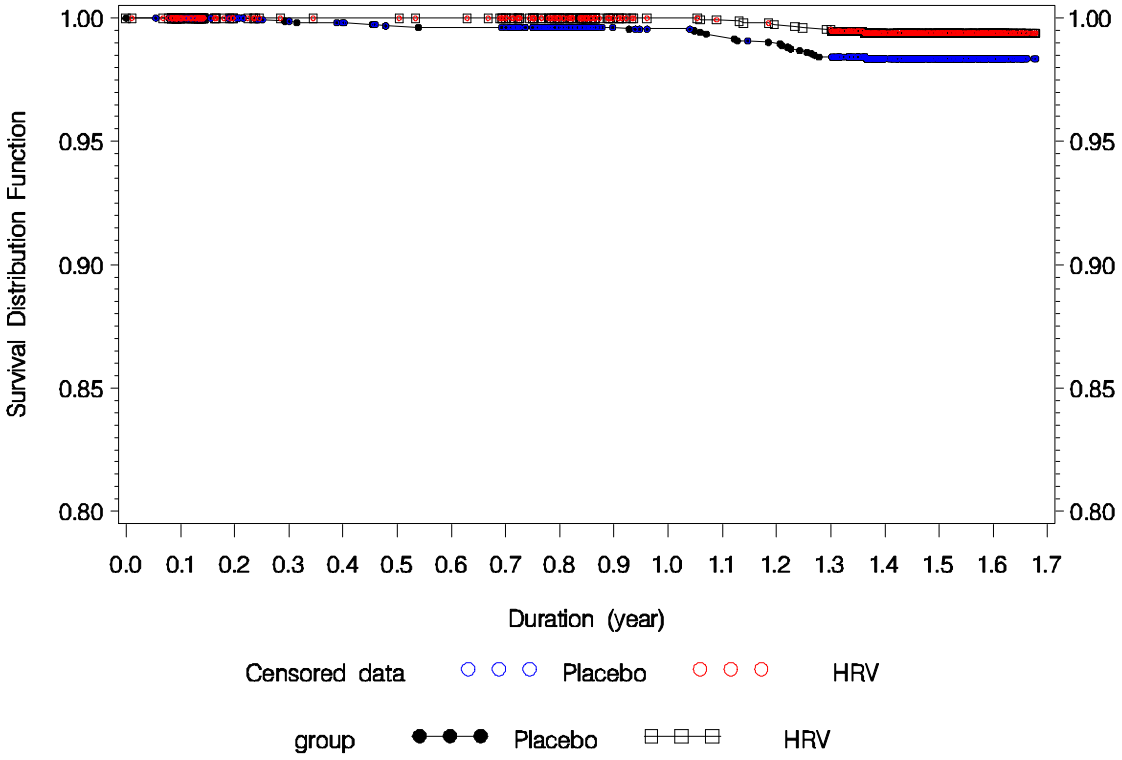

Y Axis is cut at 0.8

**Figure 28 The Kaplan Meier curve for any RV GE due to G1 wild type from Dose 1 up to Visit 7 (Total vaccinated cohort)**



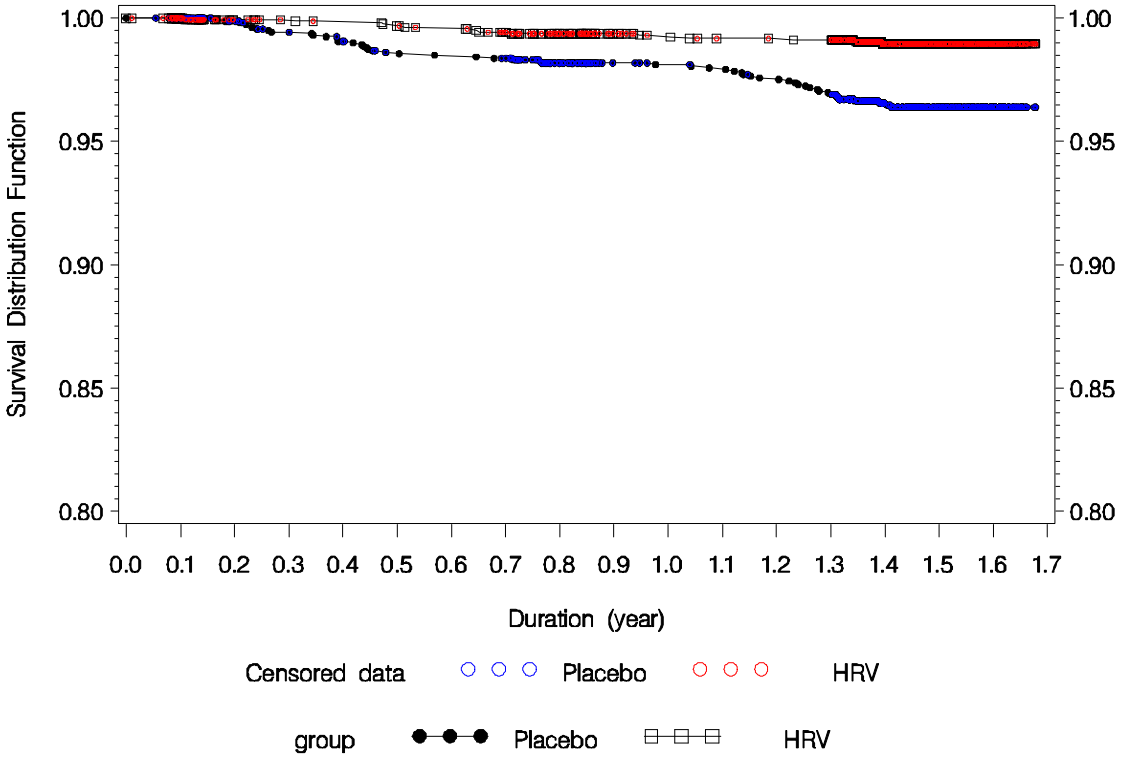

Y Axis is cut at 0.8

**Figure 29 The Kaplan Meier curve for severe RV GE due to G1 wild type from Dose 1 up to Visit 7 (Total vaccinated cohort)**




Y Axis is cut at 0.8

**Figure 30 The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from Dose 1 up to Visit 7 (Total vaccinated cohort)**




Y Axis is cut at 0.8

## 11.5.3. Characterization of GE episodes from Dose 1 up to Visit 6

### Table 142 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 N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 948 | 56.9 | 927 | 55.6 | 1875 | 56.3 |
| | 1 | 493 | 29.6 | 499 | 29.9 | 992 | 29.8 |
| | 2 | 148 | 8.9 | 162 | 9.7 | 310 | 9.3 |
| | 3 | 48 | 2.9 | 48 | 2.9 | 96 | 2.9 |
| | 4 | 19 | 1.1 | 16 | 1.0 | 35 | 1.1 |
| | 5 | 9 | 0.5 | 7 | 0.4 | 16 | 0.5 |
| | 6 | 0 | 0.0 | 6 | 0.4 | 6 | 0.2 |
| | 7 | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| | Any | 718 | 43.1 | 740 | 44.4 | 1458 | 43.7 |
| RVGE | 0 | 1636 | 98.2 | 1570 | 94.2 | 3206 | 96.2 |
| | 1 | 30 | 1.8 | 94 | 5.6 | 124 | 3.7 |
| | 2 | 0 | 0.0 | 3 | 0.2 | 3 | 0.1 |
| | Any | 30 | 1.8 | 97 | 5.8 | 127 | 3.8 |
| Severe GE | 0 | 1524 | 91.5 | 1514 | 90.8 | 3038 | 91.1 |
| | 1 | 132 | 7.9 | 139 | 8.3 | 271 | 8.1 |
| | 2 | 8 | 0.5 | 12 | 0.7 | 20 | 0.6 |
| | 3 | 2 | 0.1 | 2 | 0.1 | 4 | 0.1 |
| | Any | 142 | 8.5 | 153 | 9.2 | 295 | 8.9 |
| Severe RVGE | 0 | 1656 | 99.4 | 1634 | 98.0 | 3290 | 98.7 |
| | 1 | 10 | 0.6 | 33 | 2.0 | 43 | 1.3 |
| | Any | 10 | 0.6 | 33 | 2.0 | 43 | 1.3 |

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

### Table 143 Number of GE episodes reported from Dose 1 up to Visit 6 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| **Event** | **Severity using 20 point Vesikari scale** | **n** | **%** | **n** | **%** |
| GE | Mild (1-6) | 613 | 57.8 | 652 | 58.4 |
| | Moderate (7-10) | 285 | 26.9 | 288 | 25.8 |
| | Severe (≥11) | 154 | 14.5 | 169 | 15.1 |
| | Unknown | 9 | 0.8 | 7 | 0.6 |
| | Any | 1052 | 99.2 | 1109 | 99.4 |
| RVGE | Mild (1-6) | 12 | 40.0 | 32 | 32.0 |
| | Moderate (7-10) | 8 | 26.7 | 35 | 35.0 |
| | Severe (≥11) | 10 | 33.3 | 33 | 33.0 |
| | Any | 30 | 100 | 100 | 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

## Table 144 Percentage of GE episodes with no available stool results from Dose 1 up to Visit 6 (Total vaccinated cohort)

| | HRV N' = 1061 | | Placebo N' = 1116 | | Total N' = 2177 | |
|---|---|---|---|---|---|---|
| **Categories** | **n** | **%** | **n** | **%** | **n** | **%** |
| No stool results available | 161 | 15.2 | 146 | 13.1 | 307 | 14.1 |
| no stools collected | 161 | 15.2 | 146 | 13.1 | 307 | 14.1 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 145 Percentage of subjects with RV GE episodes from Dose 1 up to Visit 6 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** |
| Any | 30 | 1.8 | 97 | 5.8 |
| G1 WT | 3 | 0.2 | 18 | 1.1 |
| G2 | 24 | 1.4 | 73 | 4.4 |
| G3 | 1 | 0.1 | 8 | 0.5 |
| G9 | 0 | 0.0 | 1 | 0.1 |
| GX | 2 | 0.1 | 2 | 0.1 |
| P4 | 24 | 1.4 | 73 | 4.4 |
| P8 WT | 4 | 0.2 | 25 | 1.5 |
| PX | 3 | 0.2 | 1 | 0.1 |

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
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 146 Percentage of subjects with severe RV GE episodes from Dose 1 up to Visit 6 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** |
| Any | 10 | 0.6 | 33 | 2.0 |
| G1 WT | 0 | 0.0 | 6 | 0.4 |
| G2 | 8 | 0.5 | 28 | 1.7 |
| G3 | 1 | 0.1 | 2 | 0.1 |
| GX | 1 | 0.1 | 0 | 0.0 |
| P4 | 8 | 0.5 | 26 | 1.6 |
| P8 WT | 2 | 0.1 | 7 | 0.4 |
| PX | 1 | 0.1 | 1 | 0.1 |

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 severe RV GE episode whatever the serotype
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 147 Number of RV GE episodes reported from Dose 1 up to Visit 6, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=30 | | Placebo N'=100 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 3 | 3.00 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 1.00 |
| G1WT+P4 | 0 | 0.00 | 1 | 1.00 |
| G1WT+P8WT | 2 | 6.67 | 14 | 14.00 |
| G1WT+PX | 1 | 3.33 | 0 | 0.00 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 1.00 |
| G2+P4 | 23 | 76.67 | 69 | 69.00 |
| G2+P4+P8WT | 1 | 3.33 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 1.00 |
| G3+P8WT | 1 | 3.33 | 7 | 7.00 |
| G9+P8WT | 0 | 0.00 | 1 | 1.00 |
| GX | 0 | 0.00 | 1 | 1.00 |
| GX+P8WT | 0 | 0.00 | 1 | 1.00 |
| GX+PX | 2 | 6.67 | 0 | 0.00 |

WT=Wild Type
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 to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 148 Number of severe RV GE episodes reported from Dose 1 up to Visit 6, by G and P type (Total vaccinated cohort )

| Serotype | HRV N'= 10 | | Placebo N'=33 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+G2+P4 | 0 | 0.00 | 1 | 3.03 |
| G1WT+G2+P8WT | 0 | 0.00 | 1 | 3.03 |
| G1WT+P8WT | 0 | 0.00 | 4 | 12.12 |
| G2+G3+P4+P8WT | 0 | 0.00 | 1 | 3.03 |
| G2+P4 | 7 | 70.00 | 24 | 72.73 |
| G2+P4+P8WT | 1 | 10.00 | 0 | 0.00 |
| G2+PX | 0 | 0.00 | 1 | 3.03 |
| G3+P8WT | 1 | 10.00 | 1 | 3.03 |
| GX+PX | 1 | 10.00 | 0 | 0.00 |

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 severe RV GE episodes reported from dose 1 to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

**Table 149 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 (Total vaccinated cohort)**

| | | HRV N' = 30 | | Placebo N' = 100 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.1 | - | 8.8 | - |
| | SD | 3.9 | - | 4.2 | - |
| | Median | 8.0 | - | 8.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 24 | 80.0 | 63 | 63.0 |
| | 5 | 3 | 10.0 | 14 | 14.0 |
| | more than 5 days | 3 | 10.0 | 23 | 23.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 4 | 13.3 | 15 | 15.0 |
| | 4 to 5 | 13 | 43.3 | 37 | 37.0 |
| | more than 5 | 13 | 43.3 | 48 | 48.0 |
| Duration of vomiting (days) | 0 day | 17 | 56.7 | 49 | 49.0 |
| | 1 day | 4 | 13.3 | 20 | 20.0 |
| | 2 days | 6 | 20.0 | 14 | 14.0 |
| | more than 2 days | 3 | 10.0 | 17 | 17.0 |
| Max number of episodes of vomiting /day | 0 | 17 | 56.7 | 49 | 49.0 |
| | 1 | 2 | 6.7 | 12 | 12.0 |
| | 2 to 4 | 9 | 30.0 | 31 | 31.0 |
| | more than 4 | 2 | 6.7 | 8 | 8.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 8 | 26.7 | 33 | 33.0 |
| | 36.6 to 37.9°C | 13 | 43.3 | 45 | 45.0 |
| | 38.0 to 38.4°C | 6 | 20.0 | 12 | 12.0 |
| | more than 38.4°C | 3 | 10.0 | 10 | 10.0 |
| Treatment | none | 17 | 56.7 | 52 | 52.0 |
| | rehydration | 11 | 36.7 | 34 | 34.0 |
| | hospitalization | 2 | 6.7 | 14 | 14.0 |
| Dehydration | none | 17 | 56.7 | 52 | 52.0 |
| | 1 to 5% | 4 | 13.3 | 12 | 12.0 |
| | more than 5 % | 9 | 30.0 | 36 | 36.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 150 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By G1WT type (Total vaccinated cohort)**

| | | HRV N' = 3 | | Placebo N' = 19 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.0 | - | 8.6 | - |
| | SD | 3.6 | - | 3.2 | - |
| | Median | 5.0 | - | 10.0 | - |
| | Minimum | 3.0 | - | 3.0 | - |
| | Maximum | 10.0 | - | 14.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 3 | 100 | 12 | 63.2 |
| | 5 | 0 | 0.0 | 5 | 26.3 |
| | more than 5 days | 0 | 0.0 | 2 | 10.5 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 1 | 33.3 | 0 | 0.0 |
| | 4 to 5 | 1 | 33.3 | 12 | 63.2 |
| | more than 5 | 1 | 33.3 | 7 | 36.8 |
| Duration of vomiting (days) | 0 day | 3 | 100 | 9 | 47.4 |
| | 1 day | 0 | 0.0 | 5 | 26.3 |
| | 2 days | 0 | 0.0 | 2 | 10.5 |
| | more than 2 days | 0 | 0.0 | 3 | 15.8 |
| Max number of episodes of vomiting /day | 0 | 3 | 100 | 9 | 47.4 |
| | 1 | 0 | 0.0 | 2 | 10.5 |
| | 2 to 4 | 0 | 0.0 | 8 | 42.1 |
| | more than 4 | 0 | 0.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 6 | 31.6 |
| | 36.6 to 37.9°C | 1 | 33.3 | 9 | 47.4 |
| | 38.0 to 38.4°C | 1 | 33.3 | 3 | 15.8 |
| | more than 38.4°C | 1 | 33.3 | 1 | 5.3 |
| Treatment | none | 2 | 66.7 | 10 | 52.6 |
| | rehydration | 1 | 33.3 | 5 | 26.3 |
| | hospitalization | 0 | 0.0 | 4 | 21.1 |
| Dehydration | none | 2 | 66.7 | 10 | 52.6 |
| | 1 to 5% | 1 | 33.3 | 3 | 15.8 |
| | more than 5 % | 0 | 0.0 | 6 | 31.6 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 151 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By G2 type (Total vaccinated cohort)**

| | | HRV N' = 24 | | Placebo N' = 75 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.2 | - | 9.1 | - |
| | SD | 4.0 | - | 4.6 | - |
| | Median | 8.0 | - | 8.0 | - |
| | Minimum | 3.0 | - | 2.0 | - |
| | Maximum | 16.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 20 | 83.3 | 46 | 61.3 |
| | 5 | 2 | 8.3 | 8 | 10.7 |
| | more than 5 days | 2 | 8.3 | 21 | 28.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 3 | 12.5 | 13 | 17.3 |
| | 4 to 5 | 11 | 45.8 | 25 | 33.3 |
| | more than 5 | 10 | 41.7 | 37 | 49.3 |
| Duration of vomiting (days) | 0 day | 13 | 54.2 | 36 | 48.0 |
| | 1 day | 4 | 16.7 | 15 | 20.0 |
| | 2 days | 4 | 16.7 | 12 | 16.0 |
| | more than 2 days | 3 | 12.5 | 12 | 16.0 |
| Max number of episodes of vomiting /day | 0 | 13 | 54.2 | 36 | 48.0 |
| | 1 | 2 | 8.3 | 6 | 8.0 |
| | 2 to 4 | 8 | 33.3 | 25 | 33.3 |
| | more than 4 | 1 | 4.2 | 8 | 10.7 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 8 | 33.3 | 23 | 30.7 |
| | 36.6 to 37.9°C | 10 | 41.7 | 33 | 44.0 |
| | 38.0 to 38.4°C | 5 | 20.8 | 10 | 13.3 |
| | more than 38.4°C | 1 | 4.2 | 9 | 12.0 |
| Treatment | none | 12 | 50.0 | 39 | 52.0 |
| | rehydration | 10 | 41.7 | 25 | 33.3 |
| | hospitalization | 2 | 8.3 | 11 | 14.7 |
| Dehydration | none | 12 | 50.0 | 39 | 52.0 |
| | 1 to 5% | 3 | 12.5 | 7 | 9.3 |
| | more than 5 % | 9 | 37.5 | 29 | 38.7 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 152 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By G3 type (Total vaccinated cohort)**

| | | HRV N' = 1 | | Placebo N' = 8 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 11.0 | - | 8.8 | - |
| | SD | 0.0 | - | 4.2 | - |
| | Median | 11.0 | - | 8.5 | - |
| | Minimum | 11.0 | - | 2.0 | - |
| | Maximum | 11.0 | - | 16.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 1 | 100 | 5 | 62.5 |
| | 5 | 0 | 0.0 | 1 | 12.5 |
| | more than 5 days | 0 | 0.0 | 2 | 25.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 12.5 |
| | 4 to 5 | 0 | 0.0 | 4 | 50.0 |
| | more than 5 | 1 | 100 | 3 | 37.5 |
| Duration of vomiting (days) | 0 day | 0 | 0.0 | 3 | 37.5 |
| | 1 day | 0 | 0.0 | 2 | 25.0 |
| | 2 days | 1 | 100 | 2 | 25.0 |
| | more than 2 days | 0 | 0.0 | 1 | 12.5 |
| Max number of episodes of vomiting /day | 0 | 0 | 0.0 | 3 | 37.5 |
| | 1 | 0 | 0.0 | 3 | 37.5 |
| | 2 to 4 | 1 | 100 | 1 | 12.5 |
| | more than 4 | 0 | 0.0 | 1 | 12.5 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 3 | 37.5 |
| | 36.6 to 37.9°C | 0 | 0.0 | 4 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 1 | 100 | 1 | 12.5 |
| Treatment | none | 1 | 100 | 4 | 50.0 |
| | rehydration | 0 | 0.0 | 4 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 1 | 100 | 4 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 1 | 12.5 |
| | more than 5 % | 0 | 0.0 | 3 | 37.5 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

## Table 153 Characteristics of the RV GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 – By GX type (Total vaccinated cohort)

| | | HRV N' = 2 | | Placebo N' = 2 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 8.5 | - | 9.0 | - |
| | SD | 4.9 | - | 1.4 | - |
| | Median | 8.5 | - | 9.0 | - |
| | Minimum | 5.0 | - | 8.0 | - |
| | Maximum | 12.0 | - | 10.0 | - |
| Duration of looser than normal stools (days) | 0 day | 0 | 0.0 | 0 | 0.0 |
| | 1 to 4 days | 0 | 0.0 | 2 | 100 |
| | 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 days | 1 | 50.0 | 0 | 0.0 |
| Maximum number of looser than normal stools/day | 0 | 0 | 0.0 | 0 | 0.0 |
| | 1 to 3 | 0 | 0.0 | 1 | 50.0 |
| | 4 to 5 | 1 | 50.0 | 0 | 0.0 |
| | more than 5 | 1 | 50.0 | 1 | 50.0 |
| Duration of vomiting (days) | 0 day | 1 | 50.0 | 0 | 0.0 |
| | 1 day | 0 | 0.0 | 1 | 50.0 |
| | 2 days | 1 | 50.0 | 0 | 0.0 |
| | more than 2 days | 0 | 0.0 | 1 | 50.0 |
| Max number of episodes of vomiting /day | 0 | 1 | 50.0 | 0 | 0.0 |
| | 1 | 0 | 0.0 | 1 | 50.0 |
| | 2 to 4 | 0 | 0.0 | 1 | 50.0 |
| | more than 4 | 1 | 50.0 | 0 | 0.0 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 0 | 0.0 | 1 | 50.0 |
| | 36.6 to 37.9°C | 2 | 100 | 1 | 50.0 |
| | 38.0 to 38.4°C | 0 | 0.0 | 0 | 0.0 |
| | more than 38.4°C | 0 | 0.0 | 0 | 0.0 |
| Treatment | none | 2 | 100 | 1 | 50.0 |
| | rehydration | 0 | 0.0 | 1 | 50.0 |
| | hospitalization | 0 | 0.0 | 0 | 0.0 |
| Dehydration | none | 2 | 100 | 1 | 50.0 |
| | 1 to 5% | 0 | 0.0 | 0 | 0.0 |
| | more than 5 % | 0 | 0.0 | 1 | 50.0 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)
GX=G type unknown, but not vaccine strain

## Table 154 Characteristics of the GE episodes (based on Vesikari scale) reported from Dose 1 up to Visit 6 (Total vaccinated cohort)

| | | HRV N' = 1061 | | Placebo N' = 1116 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameters or Categories** | **Value or n** | **%** | **Value or n** | **%** |
| Vesikari severity score | Mean | 6.3 | - | 6.5 | - |
| | SD | 3.6 | - | 3.7 | - |
| | Median | 5.0 | - | 6.0 | - |
| | Minimum | 0.0 | - | 0.0 | - |
| | Maximum | 19.0 | - | 20.0 | - |
| Duration of looser than normal stools (days) | 0 day | 13 | 1.2 | 10 | 0.9 |
| | 1 to 4 days | 738 | 69.6 | 753 | 67.5 |
| | 5 | 109 | 10.3 | 105 | 9.4 |
| | more than 5 days | 201 | 18.9 | 248 | 22.2 |
| Maximum number of looser than normal stools/day | 0 | 13 | 1.2 | 10 | 0.9 |
| | 1 to 3 | 216 | 20.4 | 191 | 17.1 |
| | 4 to 5 | 505 | 47.6 | 562 | 50.4 |
| | more than 5 | 327 | 30.8 | 353 | 31.6 |
| Duration of vomiting (days) | 0 day | 795 | 74.9 | 835 | 74.8 |
| | 1 day | 127 | 12.0 | 143 | 12.8 |
| | 2 days | 71 | 6.7 | 55 | 4.9 |
| | more than 2 days | 68 | 6.4 | 83 | 7.4 |
| Max number of episodes of vomiting /day | 0 | 795 | 74.9 | 835 | 74.8 |
| | 1 | 84 | 7.9 | 103 | 9.2 |
| | 2 to 4 | 162 | 15.3 | 146 | 13.1 |
| | more than 4 | 20 | 1.9 | 32 | 2.9 |
| Maximum fever reported/day (Axillary) | less than 36.6°C | 495 | 46.7 | 517 | 46.3 |
| | 36.6 to 37.9°C | 436 | 41.1 | 449 | 40.2 |
| | 38.0 to 38.4°C | 53 | 5.0 | 68 | 6.1 |
| | more than 38.4°C | 77 | 7.3 | 82 | 7.3 |
| Treatment | none | 731 | 68.9 | 771 | 69.1 |
| | rehydration | 283 | 26.7 | 275 | 24.6 |
| | hospitalization | 47 | 4.4 | 70 | 6.3 |
| Dehydration | none | 731 | 68.9 | 771 | 69.1 |
| | 1 to 5% | 137 | 12.9 | 132 | 11.8 |
| | more than 5 % | 193 | 18.2 | 213 | 19.1 |

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
For each episode of GE the dehydration percentage is derived by using the following rule: Use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for >5% dehydration) or hospitalisation (hospitalised subjects will be considered to have >5% dehydration)

**Table 155 Duration (in years) of efficacy follow-up period - from Dose 1 up to Visit 6 (Total vaccinated cohort)**

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 1299 | 1293 |
| | Mean | 0.78 | 0.78 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 0.77 | 0.77 |
| | Median | 0.81 | 0.81 |
| | Q3 | 0.85 | 0.84 |
| | Maximum | 1.09 | 1.05 |

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

## 11.5.4. Vaccine efficacy during the period from Dose 1 up to Visit 6

### 11.5.4.1. Vaccine efficacy against severe RV GE

**Table 156 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) 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 | 1666 | 10 | 0.6 | 0.3 | 1.1 | 69.7 | 37.0 | 86.7 | <0.001 |
| Placebo | 1667 | 33 | 2.0 | 1.4 | 2.8 | - | - | - | - |

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

**Table 157 Percentage of subjects reporting RV GE episodes with a score greater than or equal to X on the Vesikari scale and efficacy of the vaccine from Dose 1 up to Visit 6 (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Severity using Vesikari scale | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| ≥11 | HRV | 1666 | 10 | 0.6 | 0.3 | 1.1 | 69.7 | 37.0 | 86.7 | <0.001 |
| | Placebo | 1667 | 33 | 2.0 | 1.4 | 2.8 | - | - | - | - |
| ≥12 | HRV | 1666 | 7 | 0.4 | 0.2 | 0.9 | 75.8 | 43.7 | 91.1 | <0.001 |
| | Placebo | 1667 | 29 | 1.7 | 1.2 | 2.5 | - | - | - | - |
| ≥13 | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | 85.0 | 49.4 | 97.1 | <0.001 |
| | Placebo | 1667 | 20 | 1.2 | 0.7 | 1.8 | - | - | - | - |
| ≥14 | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | 76.9 | 16.0 | 95.8 | 0.021 |
| | Placebo | 1667 | 13 | 0.8 | 0.4 | 1.3 | - | - | - | - |
| ≥15 | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 77.8 | -7.4 | 97.7 | 0.066 |
| | Placebo | 1667 | 9 | 0.5 | 0.2 | 1.0 | - | - | - | - |
| ≥16 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 87.5 | 6.7 | 99.7 | 0.039 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| ≥17 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -51.6 | 100.0 | 0.125 |
| | Placebo | 1667 | 4 | 0.2 | 0.1 | 0.6 | - | - | - | - |
| ≥18 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| ≥19 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| =20 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 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 a score greater than or equal to X on the Vesikari scale, in each group
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
P_value=Two-sided exact p_value conditional to the number of cases
X: X takes the value from 11 to 20 on the Vesikari scale

### 11.5.4.2. Vaccine efficacy against any RV GE

**Table 158 Percentage of subjects reporting any 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 | 1666 | 30 | 1.8 | 1.2 | 2.6 | 69.1 | 53.0 | 80.2 | <0.001 |
| Placebo | 1667 | 97 | 5.8 | 4.7 | 7.1 | - | - | - | - |

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

### 11.5.4.3. Vaccine efficacy against circulating RV types

**Table 159 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | 15.0 | 100.0 | 0.031 |
| | Placebo | 1667 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |
| G2 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 71.4 | 35.6 | 88.7 | 0.001 |
| | Placebo | 1667 | 28 | 1.7 | 1.1 | 2.4 | - | - | - | - |
| G3 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 50.0 | -861.0 | 99.2 | 1.000 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| GX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | Und. | Und. | Und. | 1.000 |
| | Placebo | 1667 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |
| P4 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 69.2 | 30.0 | 88.0 | 0.003 |
| | Placebo | 1667 | 26 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| P8WT | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 71.4 | -50.1 | 97.1 | 0.180 |
| | Placebo | 1667 | 7 | 0.4 | 0.2 | 0.9 | - | - | - | - |
| PX | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | -0.1 | -7754.4 | 98.7 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 10 | 0.6 | 0.3 | 1.1 | 65.5 | 27.2 | 85.0 | 0.003 |
| | Placebo | 1667 | 29 | 1.7 | 1.2 | 2.5 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain
Und. = Cannot be estimated

**Table 160 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)**

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -9.2 | 100.0 | 0.063 |
| | Placebo | 1667 | 5 | 0.3 | 0.1 | 0.7 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| G2+P4 | HRV | 1666 | 8 | 0.5 | 0.2 | 0.9 | 69.2 | 30.0 | 88.0 | 0.003 |
| | Placebo | 1667 | 26 | 1.6 | 1.0 | 2.3 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 50.0 | -861.0 | 99.2 | 1.000 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |

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

## Table 161 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by RV type (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | 83.3 | 42.9 | 96.9 | 0.001 |
| | Placebo | 1667 | 18 | 1.1 | 0.6 | 1.7 | - | - | - | - |
| G2 | HRV | 1666 | 24 | 1.4 | 0.9 | 2.1 | 67.1 | 47.2 | 80.2 | <0.001 |
| | Placebo | 1667 | 73 | 4.4 | 3.4 | 5.5 | - | - | - | - |
| G3 | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 87.5 | 6.7 | 99.7 | 0.039 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| G9 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| GX | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | -0.1 | -1280.4 | 92.7 | 1.000 |
| | Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |
| P4 | HRV | 1666 | 24 | 1.4 | 0.9 | 2.1 | 67.1 | 47.2 | 80.2 | <0.001 |
| | Placebo | 1667 | 73 | 4.4 | 3.4 | 5.5 | - | - | - | - |
| P8WT | HRV | 1666 | 4 | 0.2 | 0.1 | 0.6 | 84.0 | 53.6 | 96.0 | <0.001 |
| | Placebo | 1667 | 25 | 1.5 | 1.0 | 2.2 | - | - | - | - |
| PX | HRV | 1666 | 3 | 0.2 | 0.0 | 0.5 | -200.2 | -15658.7 | 75.9 | 0.625 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |
| Pooled Non-G1WT | HRV | 1666 | 27 | 1.6 | 1.1 | 2.3 | 67.5 | 49.2 | 79.7 | <0.001 |
| | Placebo | 1667 | 83 | 5.0 | 4.0 | 6.1 | - | - | - | - |

WT=Wild Type
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 162 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to Visit 6 by combination of G and P types (Total vaccinated cohort)

| | | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Event Type | Group | N | n | % | LL | UL | % | LL | UL | P-value |
| G1WT + P8WT | HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 86.7 | 42.6 | 98.5 | 0.002 |
| | Placebo | 1667 | 15 | 0.9 | 0.5 | 1.5 | - | - | - | - |
| G1WT+P4 | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -142.1 | 100.0 | 0.250 |
| | Placebo | 1667 | 3 | 0.2 | 0.0 | 0.5 | - | - | - | - |
| G2+P4 | HRV | 1666 | 24 | 1.4 | 0.9 | 2.1 | 66.6 | 46.4 | 79.9 | <0.001 |
| | Placebo | 1667 | 72 | 4.3 | 3.4 | 5.4 | - | - | - | - |
| G3+P8WT | HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 87.5 | 6.7 | 99.7 | 0.039 |
| | Placebo | 1667 | 8 | 0.5 | 0.2 | 0.9 | - | - | - | - |
| G9+P8WT | HRV | 1666 | 0 | 0.0 | 0.0 | 0.2 | 100.0 | -3802.3 | 100.0 | 1.000 |
| | Placebo | 1667 | 1 | 0.1 | 0.0 | 0.3 | - | - | - | - |

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

## Table 163 Percentage of subjects reporting RVGE episodes and risk difference of the vaccines from Dose 1 up to Visit 6 (Total vaccinated cohort)

| Group | | | | Person-year rate | | | Risk difference | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | n | T(Year) | n\ T | LL | UL | RD | LL | UL |
| **Any RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 30 | 1287.94 | 0.023 | 0.016 | 0.033 | 0.054 | 0.037 | 0.073 |
| Placebo | 1667 | 97 | 1251.20 | 0.078 | 0.064 | 0.095 | . | . | . |
| **Any RVGE of G1WT** | | | | | | | | | |
| HRV | 1666 | 3 | 1298.17 | 0.002 | 0.001 | 0.007 | 0.012 | 0.005 | 0.020 |
| Placebo | 1667 | 18 | 1284.85 | 0.014 | 0.009 | 0.022 | . | . | . |
| **Any RVGE of Pooled Non-G1** | | | | | | | | | |
| HRV | 1666 | 27 | 1288.92 | 0.021 | 0.014 | 0.031 | 0.045 | 0.029 | 0.062 |
| Placebo | 1667 | 83 | 1257.96 | 0.066 | 0.053 | 0.082 | . | . | . |
| **Severe RVGE of any type** | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.008 | 0.004 | 0.014 | 0.018 | 0.008 | 0.029 |
| Placebo | 1667 | 33 | 1280.13 | 0.026 | 0.018 | 0.036 | . | . | . |
| **Severe RVGE of G1 WT** | | | | | | | | | |
| HRV | 1666 | 0 | 1299.15 | 0 | Und. | Und. | 0.005 | Und. | Und. |
| Placebo | 1667 | 6 | 1290.20 | 0.005 | 0.002 | 0.010 | . | . | . |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.008 | 0.004 | 0.014 | 0.015 | 0.005 | 0.025 |
| Placebo | 1667 | 29 | 1281.92 | 0.023 | 0.016 | 0.033 | . | . | . |

WT= Wild Type
N = Number of subjects included in each group (without missing values)
n = Number of subjects with at least one event(S) in each group
T(Year)= Sum of the follow-up period expressed in years censored at the first occurrence of event in each group
n/T = person-year rate in each group
LL, UL = 95% Lower and upper confidence limits
RD = Risk difference (Placebo - HRV) - 95% CI: By the method proposed by Zou and Donner
Und. = cannot be estimated

**Table 164 Percentage of subject reporting RV GE episodes and efficacy of the vaccine from Dose 1 up to Visit 6 by Cox method (Total vaccinated cohort)**

| | | | | Person-year rate | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | 95% CI | | |
| Group | N | n | T (year) | n/T | LL | UL | % | LL | UL | P-Value |
| **Any RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 30 | 1287.94 | 0.02 | 0.02 | 0.03 | 69.89 | 54.66 | 80.01 | <0.001 |
| Placebo | 1667 | 97 | 1251.20 | 0.08 | 0.06 | 0.09 | - | - | - | - |
| **Any RVGE of G1WT** | | | | | | | | | | |
| HRV | 1666 | 3 | 1298.17 | 0.00 | 0.00 | 0.01 | 83.45 | 43.84 | 95.12 | 0.004 |
| Placebo | 1667 | 18 | 1284.85 | 0.01 | 0.01 | 0.02 | - | - | - | - |
| **Any RVGE of Pooled Non-G1WT** | | | | | | | | | | |
| HRV | 1666 | 27 | 1288.92 | 0.02 | 0.01 | 0.03 | 68.19 | 50.90 | 79.40 | <0.001 |
| Placebo | 1667 | 83 | 1257.96 | 0.07 | 0.05 | 0.08 | - | - | - | - |
| **Severe RVGE of any type** | | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.01 | 0.00 | 0.01 | 70.01 | 39.15 | 85.22 | <0.001 |
| Placebo | 1667 | 33 | 1280.13 | 0.03 | 0.02 | 0.04 | - | - | - | - |
| **Severe RVGE of G1 WT** | | | | | | | | | | |
| HRV | 1666 | 0 | 1299.15 | 0.00 | Und. | Und. | 100.00 | Und. | 100.00 | 0.994 |
| Placebo | 1667 | 6 | 1290.20 | 0.00 | 0.00 | 0.01 | - | - | - | - |
| **Severe RVGE of Pooled Non-G1 WT** | | | | | | | | | | |
| HRV | 1666 | 10 | 1296.19 | 0.01 | 0.00 | 0.01 | 65.83 | 29.88 | 83.35 | 0.003 |
| Placebo | 1667 | 29 | 1281.92 | 0.02 | 0.02 | 0.03 | - | - | - | - |

WT=Wild Type
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 of the Wald test from a Cox regression model to test H0 = [VE=0%] (Y = Time to Event)
Und. = cannot be estimated

### 11.5.4.4. Vaccine efficacy against hospitalisation due to RV

**Table 165 Percentage of subjects reporting RVGE episode requiring hospitalisation 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 | 1666 | 2 | 0.1 | 0.0 | 0.4 | 85.7 | 37.8 | 98.4 | 0.004 |
| Placebo | 1667 | 14 | 0.8 | 0.5 | 1.4 | - | - | - | - |

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

**Table 166 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 | 1666 | 13 | 0.8 | 0.4 | 1.3 | 72.9 | 49.2 | 86.5 | <0.001 |
| Placebo | 1667 | 48 | 2.9 | 2.1 | 3.8 | - | - | - | - |

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

### 11.5.4.5. Vaccine efficacy against all cause GE

**Table 167 Percentage of subjects reporting all cause of 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 | 1666 | 718 | 43.1 | 40.7 | 45.5 | 2.9 | -7.7 | 12.5 | 0.590 |
| Placebo | 1667 | 740 | 44.4 | 42.0 | 46.8 | - | - | - | - |

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

**Table 168 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) 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 | 1666 | 142 | 8.5 | 7.2 | 10.0 | 7.1 | -17.5 | 26.6 | 0.564 |
| Placebo | 1667 | 153 | 9.2 | 7.8 | 10.7 | - | - | - | - |

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

## Table 169 Percentage of subjects reporting all cause of GE episode requiring hospitalisation 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 | 1666 | 43 | 2.6 | 1.9 | 3.5 | 34.8 | 2.8 | 56.7 | 0.035 |
| Placebo | 1667 | 66 | 4.0 | 3.1 | 5.0 | - | - | - | - |

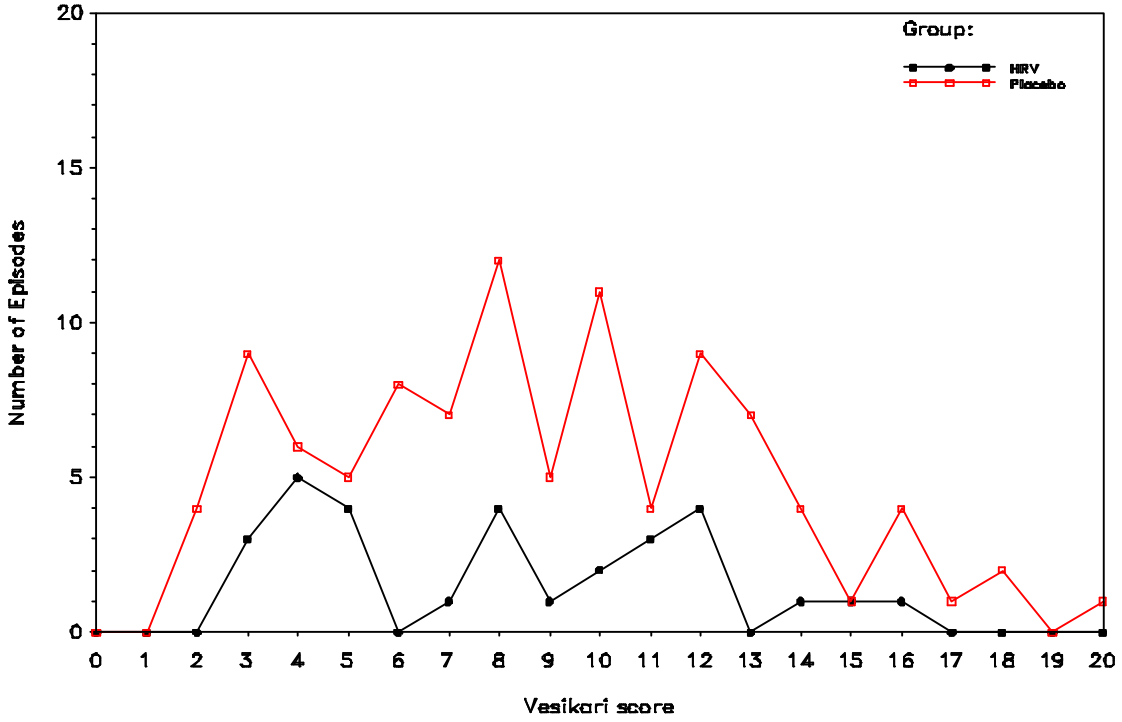
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

## Table 170 Percentage of subjects hospitalized and/or treated re-hydration therapy due to all cause of 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 | 1666 | 272 | 16.3 | 14.6 | 18.2 | 7.1 | -9.9 | 21.5 | 0.404 |
| Placebo | 1667 | 293 | 17.6 | 15.8 | 19.5 | - | - | - | - |

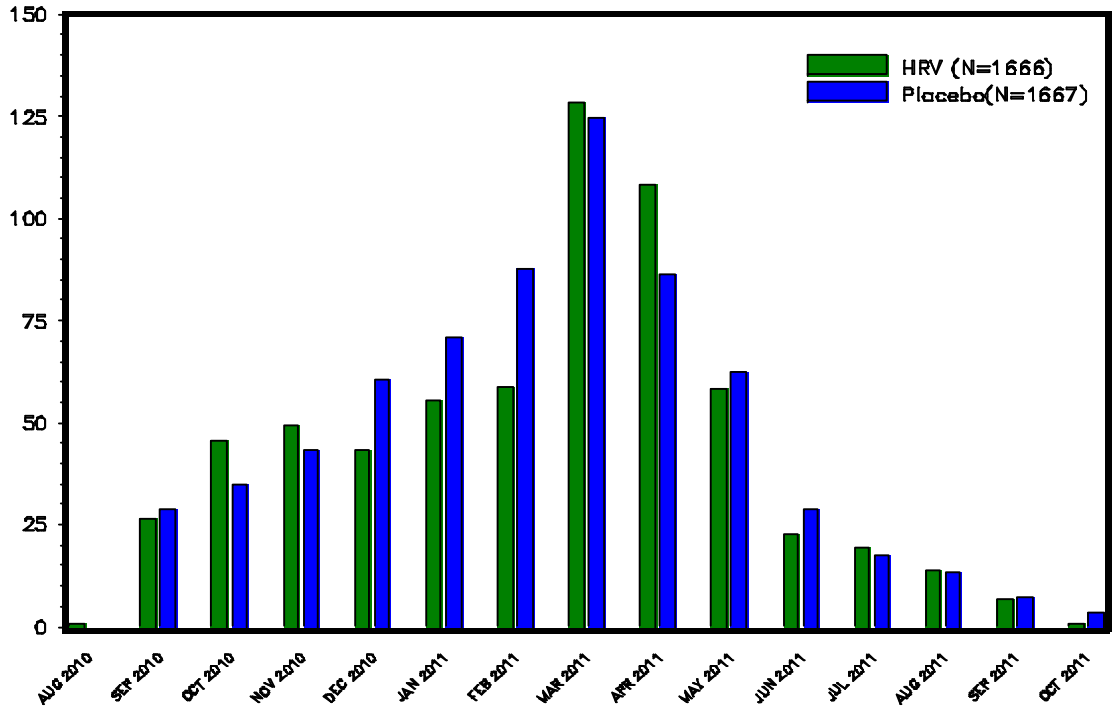
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Figure 31 Distribution of Vesikari score for RV GE episodes reported from Dose 1 up to Visit 6 (Total vaccinated cohort)**



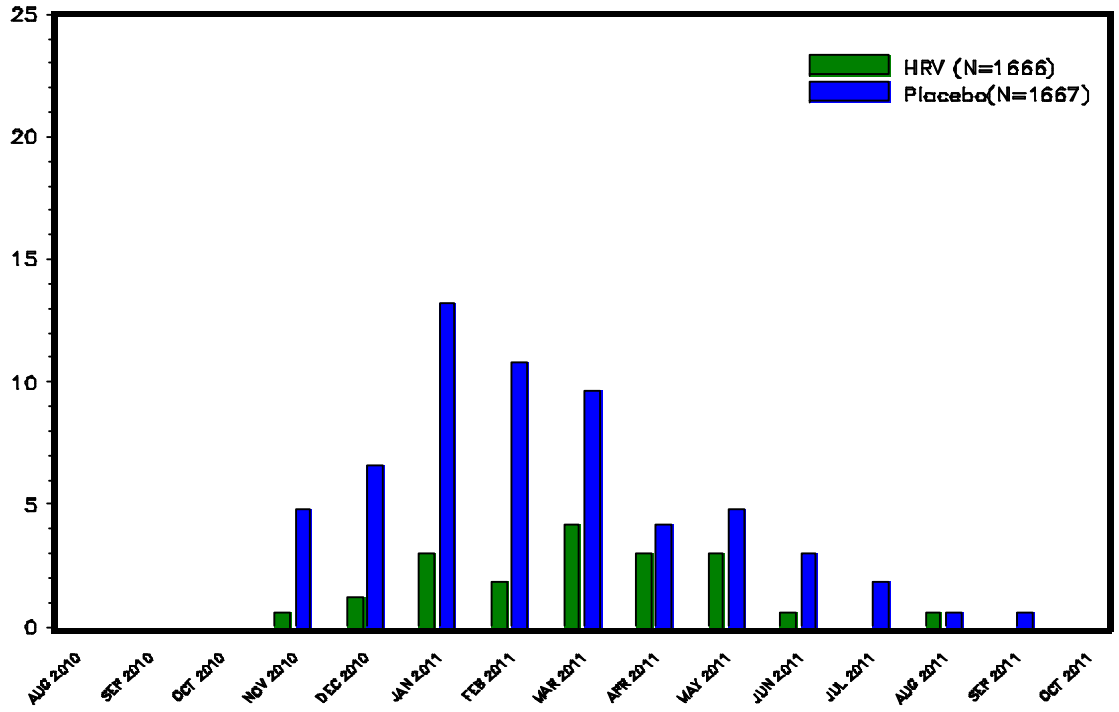

X axis = Score for each episodes computed based on the Vesikari severity scoring scale
Y Axis = Number of episodes of the event reported during the considered time period

**Figure 32 Seasonal distribution of GE episodes reported from Dose 1 up to Visit 6 for HRV group and placebo group (Total vaccinated cohort)**



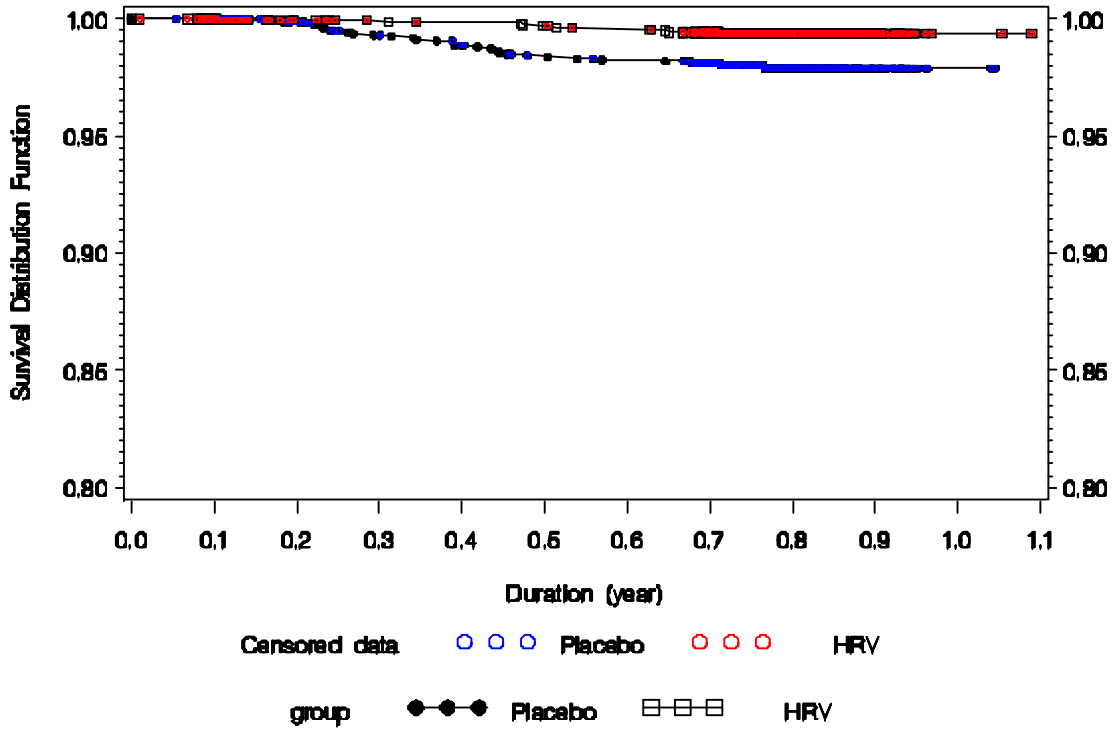

X axis = Start date of the GE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in the each group

**Figure 33 Seasonal distribution of RVGE episodes reported from Dose 1 up to Visit 6 for HRV group and placebo group (Total vaccinated cohort)**



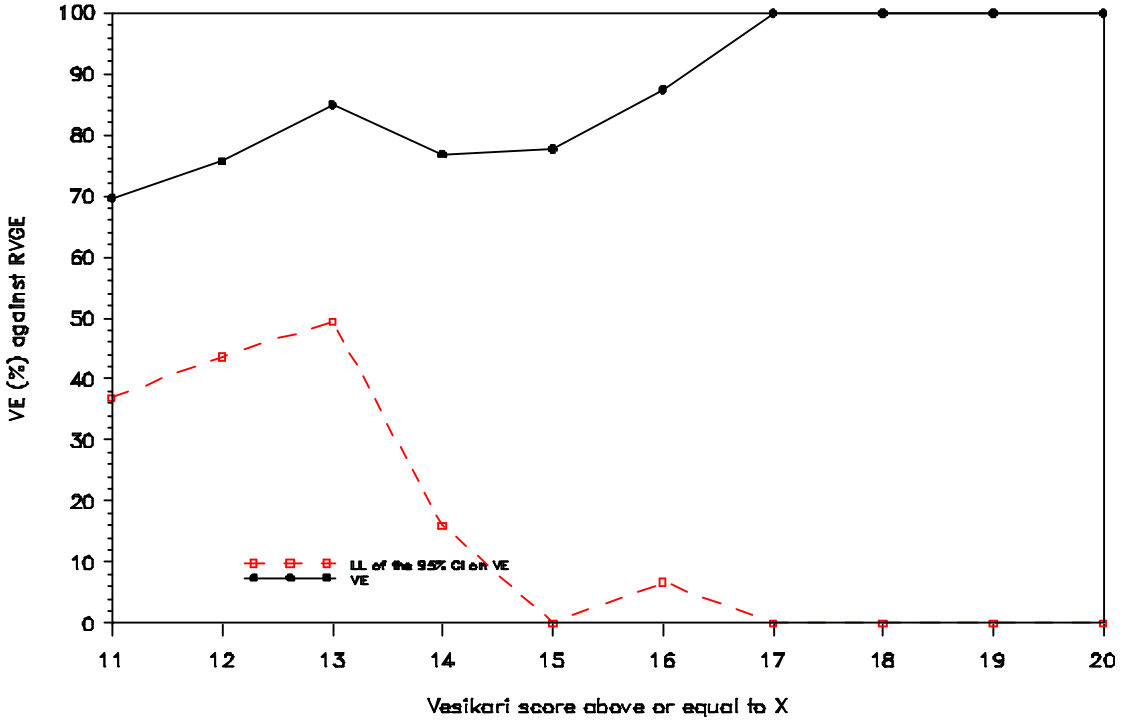

X axis = Start date of the RVGE episodes
Y Axis = Number of episodes per 1000 subjects
N=Number of subjects included in the each group

**Figure 34 The Kaplan Meier curve for severe RV GE from Dose 1 up to Visit 6 (Total vaccinated cohort)**



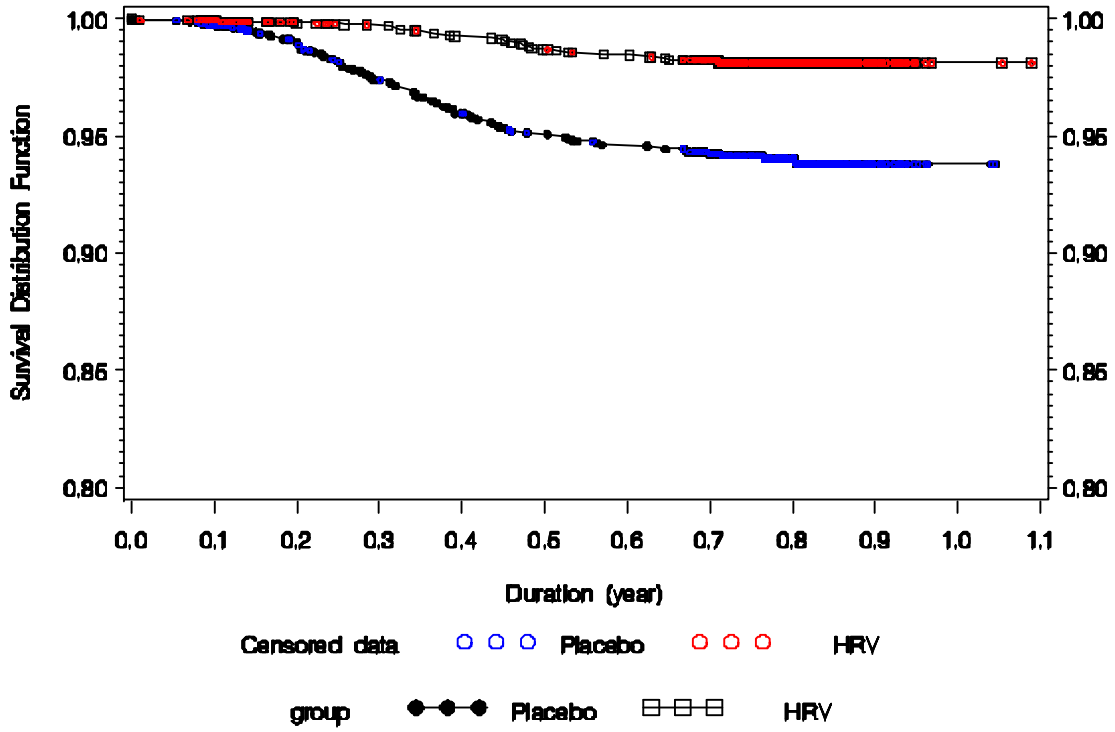

Y Axis is cut at 0.8

**Figure 35 Efficacy of the vaccine against RVGE episodes with a score greater than or equal to X from dose 1 to visit 6 (Total vaccinated cohort)**



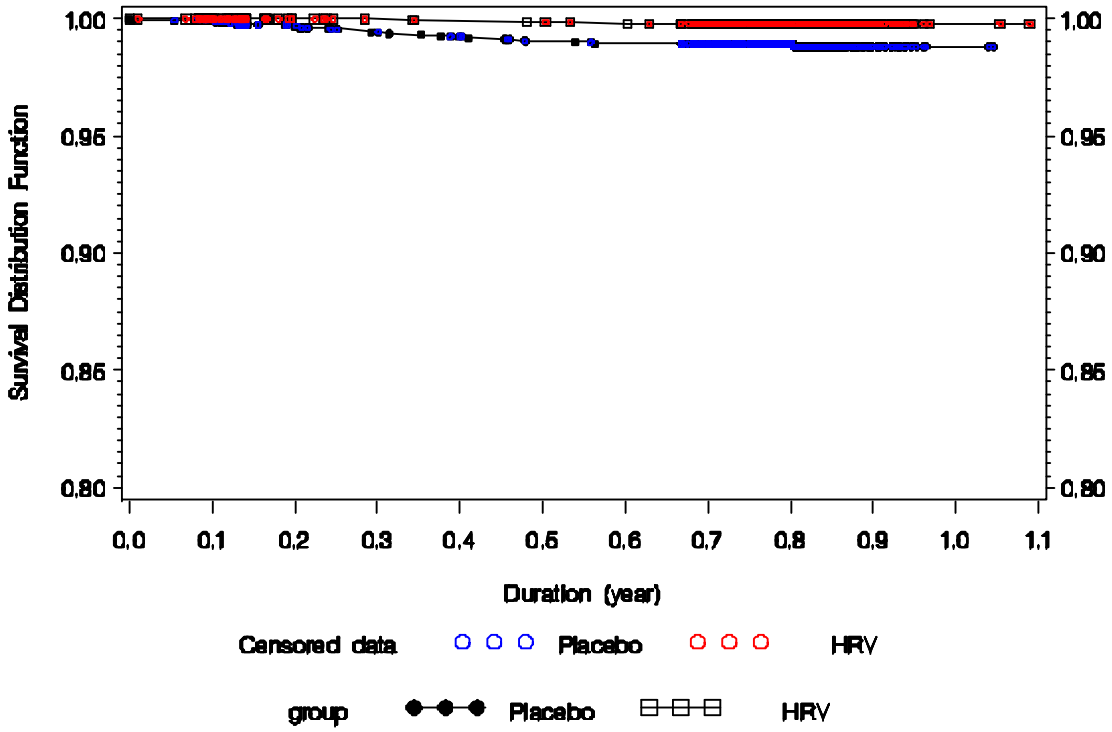

X Axis is cut at 11
Y Axis is cut at 0
X: X takes the value from 11 to 20 on the Vesikari scale

**Figure 36 The Kaplan Meier curve for any RV GE from Dose 1 up to Visit 6 (Total vaccinated cohort)**



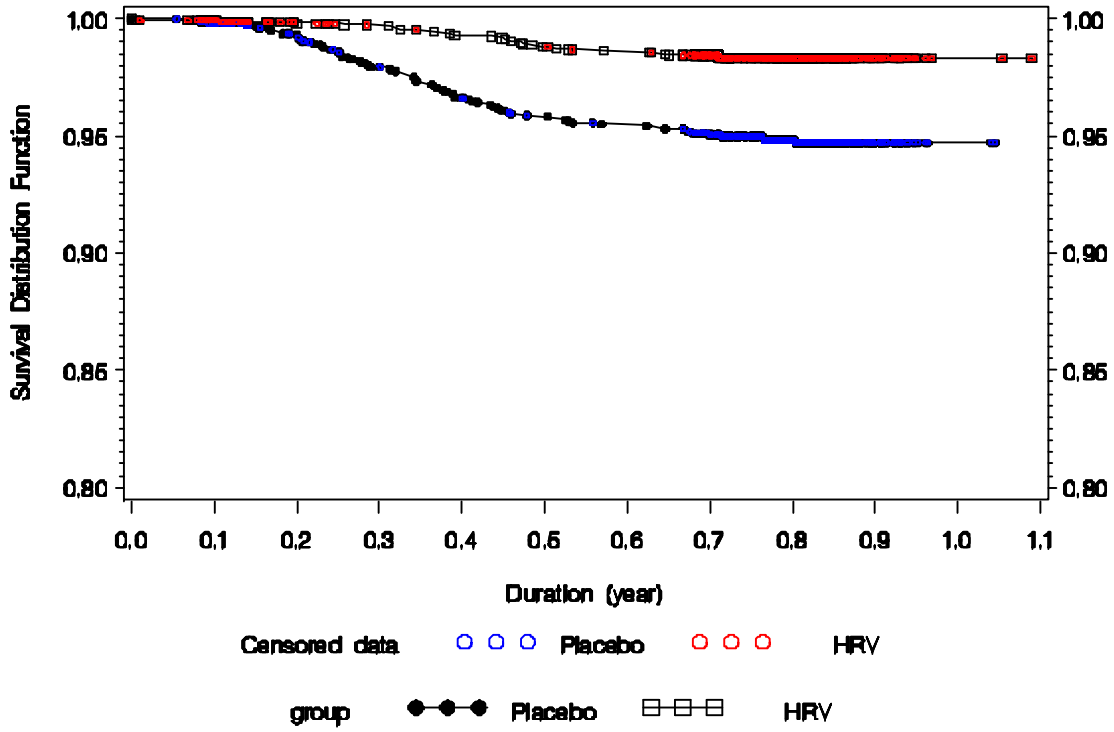

Y Axis is cut at 0.8

**Figure 37 The Kaplan Meier curve for any RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)**



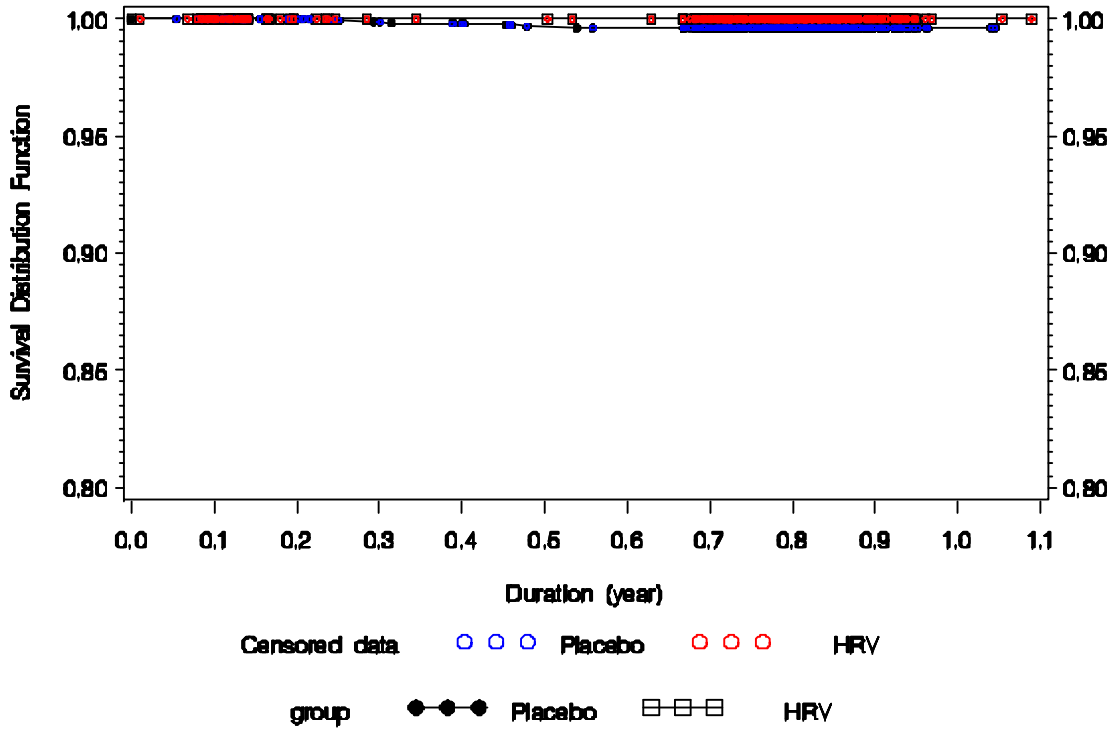

Y Axis is cut at 0.8

**Figure 38 The Kaplan Meier curve for any RV GE due to pooled non-G1 types from Dose 1 up to Visit 6 (Total vaccinated cohort)**



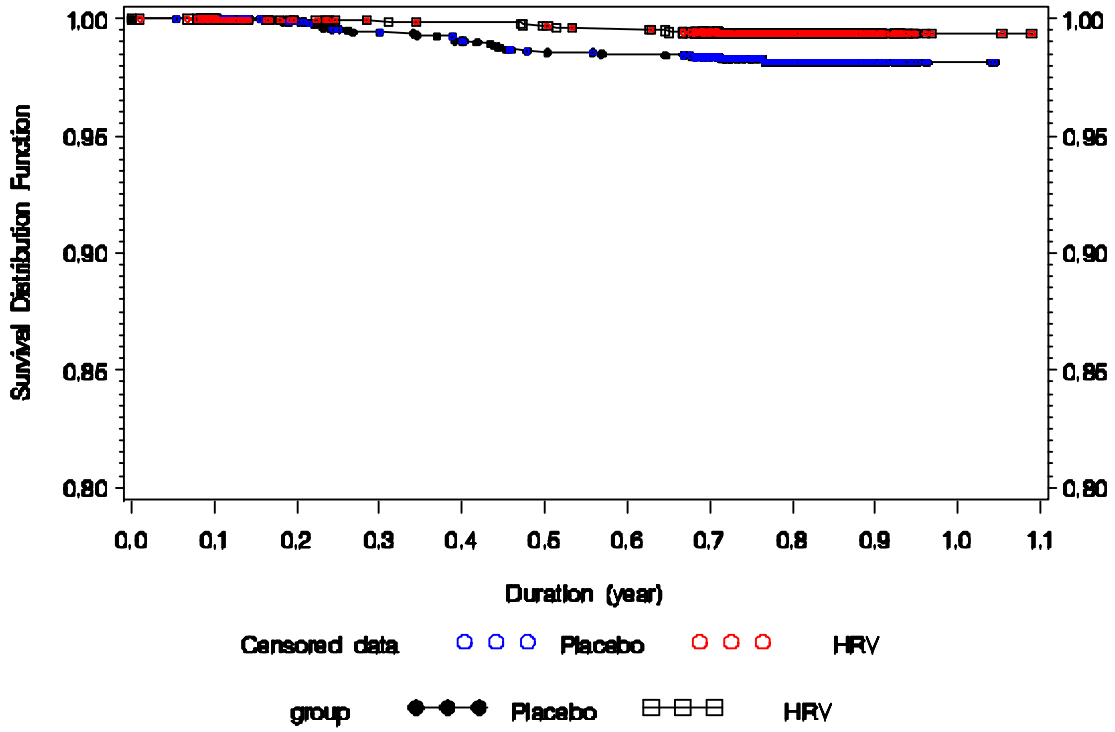

Y Axis is cut at 0.8

**Figure 39 The Kaplan Meier curve for severe RV GE due to G1 wild type from Dose 1 up to Visit 6 (Total vaccinated cohort)**




Y Axis is cut at 0.8

**Figure 40** **The Kaplan Meier curve for severe RV GE due to pooled non-G1 types from Dose 1 up to Visit 6 (Total vaccinated cohort)**




Y Axis is cut at 0.8

## 11.5.5. Characterization of GE episodes from Dose 1 up to before Dose 2

**Table 171** **Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Number of episodes** | **n** | **%** | **n** | **%** | **n** | **%** |
| GE | 0 | 1515 | 90.9 | 1507 | 90.4 | 3022 | 90.7 |
| | 1 | 140 | 8.4 | 154 | 9.2 | 294 | 8.8 |
| | 2 | 10 | 0.6 | 5 | 0.3 | 15 | 0.5 |
| | 3 | 1 | 0.1 | 1 | 0.1 | 2 | 0.1 |
| | Any | 151 | 9.1 | 160 | 9.6 | 311 | 9.3 |
| RVGE | 0 | 1665 | 99.9 | 1665 | 99.9 | 3330 | 99.9 |
| | 1 | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| | Any | 1 | 0.1 | 2 | 0.1 | 3 | 0.1 |
| Severe GE | 0 | 1652 | 99.2 | 1643 | 98.6 | 3295 | 98.9 |
| | 1 | 14 | 0.8 | 24 | 1.4 | 38 | 1.1 |
| | Any | 14 | 0.8 | 24 | 1.4 | 38 | 1.1 |
| Severe RVGE | 0 | 1666 | 100 | 1667 | 100 | 3333 | 100 |
| | Any | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

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

## Table 172 Number of GE episodes reported Dose 1 up to before Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 99 | 60.7 | 100 | 59.9 |
| | Moderate (7-10) | 41 | 25.2 | 38 | 22.8 |
| | Severe (≥11) | 14 | 8.6 | 24 | 14.4 |
| | Unknown | 9 | 5.5 | 5 | 3.0 |
| | Any | 154 | 94.5 | 162 | 97.0 |
| RVGE | Mild (1-6) | 1 | 100 | 1 | 50.0 |
| | Moderate (7-10) | 0 | 0.0 | 1 | 50.0 |
| | Any | 1 | 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

## Table 173 Percentage of GE episodes with no available stool results Dose 1 up to before Dose 2 (Total vaccinated cohort)

| | HRV N' = 163 | | Placebo N' = 167 | | Total N' = 330 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 75 | 46.0 | 63 | 37.7 | 138 | 41.8 |
| no stools collected | 75 | 46.0 | 63 | 37.7 | 138 | 41.8 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 174 Percentage of subjects with RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| Characteristics | n | % | n | % |
| Any | 1 | 0.1 | 2 | 0.1 |
| G1 WT | 0 | 0.0 | 1 | 0.1 |
| G2 | 1 | 0.1 | 1 | 0.1 |
| P4 | 1 | 0.1 | 1 | 0.1 |
| P8 WT | 0 | 0.0 | 1 | 0.1 |

N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype
Any =Number of subject reporting at least one RV GE episode whatever the serotype
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 175 Percentage of subjects with severe RV GE episodes Dose 1 up to before Dose 2 by G and P type (Total vaccinated cohort)

No record exists

## Table 176 Number of RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=1 | | Placebo N'=2 | |
|---|---|---|---|---|
| | n | % | n | % |
| G1WT+P8WT | 0 | 0.00 | 1 | 50.00 |
| G2+P4 | 1 | 100.0 | 1 | 50.00 |

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 to visit 6
WT=Wild Type
GX=G type unknown, but not vaccine strain
PX=P type unknown, but not vaccine strain

## Table 177 Number of severe RV GE episodes reported Dose 1 up to before Dose 2, by G and P type (Total vaccinated cohort)

No record exists for this table

## Table 178 Duration (in years) of efficacy follow-up period - Dose 1 up to before Dose 2 (Total vaccinated cohort)

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 148.8 | 148.8 |
| | Mean | 0.09 | 0.09 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 0.08 | 0.08 |
| | Median | 0.08 | 0.08 |
| | Q3 | 0.09 | 0.09 |
| | Maximum | 0.79 | 0.76 |

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

## 11.5.6. Vaccine efficacy during the period from Dose 1 before Dose 2

### 11.5.6.1. Vaccine efficacy against severe RV GE

**Table 179 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

No record exists for this table

### 11.5.6.2. Vaccine efficacy against any RV GE

**Table 180 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | 50.0 | -861.0 | 99.2 | 1.000 |
| Placebo | 1667 | 2 | 0.1 | 0.0 | 0.4 | - | - | - | - |

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

### 11.5.6.3. Vaccine efficacy against hospitalisation due to RV

**Table 181 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

No record exists for this table

### 11.5.6.4. Vaccine efficacy against all cause GE

**Table 182 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 151 | 9.1 | 7.7 | 10.5 | 5.6 | -18.7 | 24.9 | 0.654 |
| Placebo | 1667 | 160 | 9.6 | 8.2 | 11.1 | - | - | - | - |

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

**Table 183 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine Dose 1 up to before Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 14 | 0.8 | 0.5 | 1.4 | 41.6 | -17.5 | 72.1 | 0.144 |
| Placebo | 1667 | 24 | 1.4 | 0.9 | 2.1 | - | - | - | - |

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

## 11.5.7. Characterization of GE episodes from Dose 1 up to 2 weeks post dose 2

**Table 184 Percentage of subjects who reported GE episodes RV GE episodes severe GE episodes and severe RVGE episodes from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort )**

| | | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|---|
| Characteristics | Number of episodes | n | % | n | % | n | % |
| GE | 0 | 1450 | 87.0 | 1450 | 87.0 | 2900 | 87.0 |
| | 1 | 190 | 11.4 | 196 | 11.8 | 386 | 11.6 |
| | 2 | 22 | 1.3 | 18 | 1.1 | 40 | 1.2 |
| | 3 | 4 | 0.2 | 2 | 0.1 | 6 | 0.2 |
| | 4 | 0 | 0.0 | 1 | 0.1 | 1 | 0.0 |
| | Any | 216 | 13.0 | 217 | 13.0 | 433 | 13.0 |
| RVGE | 0 | 1664 | 99.9 | 1661 | 99.6 | 3325 | 99.8 |
| | 1 | 2 | 0.1 | 6 | 0.4 | 8 | 0.2 |
| | Any | 2 | 0.1 | 6 | 0.4 | 8 | 0.2 |
| Severe GE | 0 | 1646 | 98.8 | 1635 | 98.1 | 3281 | 98.4 |
| | 1 | 20 | 1.2 | 32 | 1.9 | 52 | 1.6 |
| | Any | 20 | 1.2 | 32 | 1.9 | 52 | 1.6 |
| Severe RVGE | 0 | 1665 | 99.9 | 1667 | 100 | 3332 | 100 |
| | 1 | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| | Any | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |

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

## Table 185 Number of GE episodes reported from Dose 1 up to 2 weeks post-Dose 2 by severity using the 20-point Vesikari scale (Total vaccinated cohort)

| | | HRV | | Placebo | |
|---|---|---|---|---|---|
| Event | Severity using 20 point Vesikari scale | n | % | n | % |
| GE | Mild (1-6) | 156 | 63.4 | 146 | 60.3 |
| | Moderate (7-10) | 61 | 24.8 | 58 | 24.0 |
| | Severe (≥11) | 20 | 8.1 | 32 | 13.2 |
| | Unknown | 9 | 3.7 | 6 | 2.5 |
| | Any | 237 | 96.3 | 236 | 97.5 |
| RVGE | Mild (1-6) | 1 | 50.0 | 2 | 33.3 |
| | Moderate (7-10) | 0 | 0.0 | 4 | 66.7 |
| | Severe (≥11) | 1 | 50.0 | 0 | 0.0 |
| | Any | 2 | 100 | 6 | 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

## Table 186 Percentage of GE episodes with no available stool results from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

| | HRV N' = 246 | | Placebo N' = 242 | | Total N' = 488 | |
|---|---|---|---|---|---|---|
| Categories | n | % | n | % | n | % |
| No stool results available | 115 | 46.7 | 97 | 40.1 | 212 | 43.4 |
| no stools collected | 115 | 46.7 | 97 | 40.1 | 212 | 43.4 |
| stools collected but no results available | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

## Table 187 Percentage of subjects with RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| Characteristics | n | % | n | % |
| Any | 2 | 0.1 | 6 | 0.4 |
| G1 wild type | 0 | 0.0 | 3 | 0.2 |
| G2 | 2 | 0.1 | 3 | 0.2 |
| P4 | 2 | 0.1 | 4 | 0.2 |
| P8 wild type | 0 | 0.0 | 2 | 0.1 |

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

## Table 188 Percentage of subjects with severe RV GE episodes from Dose 1 up to 2 weeks post-Dose 2 by G and P type (Total vaccinated cohort)

| | HRV N = 1666 | | Placebo N = 1667 | |
|---|---|---|---|---|
| **Characteristics** | **n** | **%** | **n** | **%** |
| Any | 1 | 0.1 | 0 | 0.0 |
| G2 | 1 | 0.1 | 0 | 0.0 |
| P4 | 1 | 0.1 | 0 | 0.0 |

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 severe RV GE episode whatever the serotype

## Table 189 Number of RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=2 | | Placebo N'=6 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G1WT+P4 | 0 | 0.00 | 1 | 16.67 |
| G1WT+P8WT | 0 | 0.00 | 2 | 33.33 |
| G2+P4 | 2 | 100.0 | 3 | 50.00 |

WT=Wild Type
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 up to 2 weeks post dose 2

## Table 190 Number of severe RV GE episodes reported from Dose 1 up to 2 weeks post-Dose 2, by G and P type (Total vaccinated cohort)

| Serotype | HRV N'=1 | | Placebo N'=0 | |
|---|---|---|---|---|
| | **n** | **%** | **n** | **%** |
| G2+P4 | 1 | 100.0 | 0 | 0.00 |

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 severe RV GE episodes reported from dose 1 up to 2 weeks post dose 2

## Table 191 Duration (in years) of efficacy follow-up period from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)

| | | HRV N = 1666 | Placebo N = 1667 |
|---|---|---|---|
| **Characteristics** | **Parameters** | **Value** | **Value** |
| Duration in years | Sum | 210.1 | 210.0 |
| | Mean | 0.13 | 0.13 |
| | Minimum | 0.01 | 0.05 |
| | Q1 | 0.12 | 0.12 |
| | Median | 0.12 | 0.12 |
| | Q3 | 0.13 | 0.13 |
| | Maximum | 0.79 | 0.76 |

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

## 11.5.8. Vaccine efficacy during the period from Dose 1 up to 2 weeks post dose 2

### 11.5.8.1. Vaccine efficacy against severe RV GE

**Table 192 Percentage of subjects reporting severe (Vesikari score greater than or equal to 11) RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 1 | 0.1 | 0.0 | 0.3 | Und. | Und. | Und. | 1.000 |
| Placebo | 1667 | 0 | 0.0 | 0.0 | 0.2 | - | - | - | - |

N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits
Und = Can not be estimated

### 11.5.8.2. Vaccine efficacy against any RV GE

**Table 193 Percentage of subjects reporting any RVGE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| Group | N | n | % | LL | UL | % | LL | UL | P-value |
| HRV | 1666 | 2 | 0.1 | 0.0 | 0.4 | 66.6 | -86.5 | 96.7 | 0.289 |
| Placebo | 1667 | 6 | 0.4 | 0.1 | 0.8 | - | - | - | - |

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

### 11.5.8.3. Vaccine efficacy against hospitalisation due to RV

**Table 194 Percentage of subjects reporting RVGE episode requiring hospitalisation and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

No record exists for this table

### 11.5.8.4. Vaccine efficacy against all cause GE

**Table 195 Percentage of subjects reporting all cause of GE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1666 | 216 | 13.0 | 11.4 | 14.7 | 0.4 | -20.8 | 17.9 | 1.000 |
| Placebo | 1667 | 217 | 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
P-value = Two sided Exact P-value conditional to number of cases
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 95 % Lower and Upper confidence limits

**Table 196 Percentage of subjects reporting all cause of severe (Vesikari score greater than or equal to 11) GE episode and efficacy of the vaccine from Dose 1 up to 2 weeks post-Dose 2 (Total vaccinated cohort)**

| | | | n/N | | | VE | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Group** | **N** | **n** | **%** | **LL** | **UL** | **%** | **LL** | **UL** | **P-value** |
| HRV | 1666 | 20 | 1.2 | 0.7 | 1.8 | 37.5 | -12.7 | 66.1 | 0.127 |
| Placebo | 1667 | 32 | 1.9 | 1.3 | 2.7 | - | - | - | - |

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

## 11.6. Safety Results

### 11.6.1. Total vaccinated cohort analysis

**Table 197 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort)**

| | HRV N = 1666 | | Placebo N = 1667 | | Total N = 3333 | |
|---|---|---|---|---|---|---|
| **Total number of doses received** | **n** | **%** | **n** | **%** | **n** | **%** |
| 1 | 67 | 4.0 | 70 | 4.2 | 137 | 4.1 |
| 2 | 1599 | 96.0 | 1597 | 95.8 | 3196 | 95.9 |
| Any | 1666 | 100 | 1667 | 100 | 3333 | 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

## Table 198 Number and percentage of subjects who received study vaccine doses (Total vaccinated cohort- except immunogenicity sub-cohorts)

| | HRV N = 1513 | | Placebo N = 1514 | | Total N = 3027 | |
|---|---|---|---|---|---|---|
| Total number of doses received | n | % | n | % | n | % |
| 1 | 64 | 4.2 | 68 | 4.5 | 132 | 4.4 |
| 2 | 1449 | 95.8 | 1446 | 95.5 | 2895 | 95.6 |
| Any | 1513 | 100 | 1514 | 100 | 3027 | 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

## Table 199 Number and percentage of subjects who received study vaccine doses by vaccine (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | HRV DTPA VACCINE N = 153 | | HRV OPV N = 153 | | HRV ROTARIX N = 153 | | Placebo DTPA VACCINE N = 153 | | Placebo OPV N = 153 | | Placebo PLACEBO N = 153 | | Total DTPA VACCINE N = 306 | | Total OPV N = 306 | | Total PLACEBO N = 306 | | Total ROTARIX N = 306 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total number of doses received | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| 0 | 3 | 2.0 | 0 | 0.0 | 0 | 0.0 | 2 | 1.3 | 0 | 0.0 | 0 | 0.0 | 5 | 1.6 | 0 | 0.0 | 153 | 50.0 | 153 | 50.0 |
| 1 | 1 | 0.7 | 3 | 2.0 | 3 | 2.0 | 1 | 0.7 | 2 | 1.3 | 2 | 1.3 | 2 | 0.7 | 5 | 1.6 | 2 | 0.7 | 3 | 1.0 |
| 2 | 1 | 0.7 | 1 | 0.7 | 150 | 98.0 | 2 | 1.3 | 1 | 0.7 | 151 | 98.7 | 3 | 1.0 | 2 | 0.7 | 151 | 49.3 | 150 | 49.0 |
| 3 | 148 | 96.7 | 149 | 97.4 | 0 | 0.0 | 148 | 96.7 | 150 | 98.0 | 0 | 0.0 | 296 | 96.7 | 299 | 97.7 | 0 | 0.0 | 0 | 0.0 |
| Any | 150 | 98.0 | 153 | 100 | 153 | 100 | 151 | 98.7 | 153 | 100 | 153 | 100 | 301 | 98.4 | 306 | 100 | 153 | 50.0 | 153 | 50.0 |

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

## Table 200 Compliance in returning symptom sheets (Total vaccinated cohort- except immunogenicity sub cohort 2)

| Dose | Group | Number of doses | Doses NOT according to protocol | Number of general SS | Compliance % general SS |
|---|---|---|---|---|---|
| 1 | HRV | 1513 | 0 | 1485 | 98.1 |
| | Placebo | 1514 | 0 | 1483 | 98.0 |
| 2 | HRV | 1449 | 1 | 1448 | 99.9 |
| | Placebo | 1446 | 0 | 1446 | 100 |

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

**Table 201 Compliance in returning symptom sheets (Total vaccinated cohort- Immunogenicity sub cohort 2)**

| Dose | Group | Number of doses | Doses NOT according to protocol | Number of general SS | Compliance % general SS | Number of local SS | Compliance % local SS |
|---|---|---|---|---|---|---|---|
| 1 | HRV | 153 | 0 | 150 | 98.0 | 0 | 0.0 |
| | Placebo | 153 | 0 | 151 | 98.7 | 0 | 0.0 |
| 2 | HRV | 150 | 0 | 149 | 99.3 | 149 | 99.3 |
| | Placebo | 151 | 0 | 150 | 99.3 | 150 | 99.3 |

SS = Symptom sheets used for the collection of local and general solicited AEs
Compliance % = (number of doses with symptom sheet return / number of administered doses) X 100
*Local symptom sheet for 1st dose of DTPa which is co-administered with 2nd dose of HRV / Placebo

### 11.6.1.1. Overall incidence of adverse events

**Table 202 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0 - 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 496 | 32.8 | 30.4 | 35.2 |
| | Placebo | 1514 | 562 | 37.1 | 34.7 | 39.6 |
| Dose 2 | HRV | 1449 | 386 | 26.6 | 24.4 | 29.0 |
| | Placebo | 1446 | 389 | 26.9 | 24.6 | 29.3 |
| Overall/dose | HRV | 2962 | 882 | 29.8 | 28.1 | 31.5 |
| | Placebo | 2960 | 951 | 32.1 | 30.4 | 33.8 |
| Overall/subject | HRV | 1513 | 669 | 44.2 | 41.7 | 46.8 |
| | Placebo | 1514 | 716 | 47.3 | 44.8 | 49.8 |

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

## Table 203 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 589 | 38.9 | 36.5 | 41.4 |
| | Placebo | 1514 | 645 | 42.6 | 40.1 | 45.1 |
| Dose 2 | HRV | 1449 | 448 | 30.9 | 28.5 | 33.4 |
| | Placebo | 1446 | 448 | 31.0 | 28.6 | 33.4 |
| Overall/dose | HRV | 2962 | 1037 | 35.0 | 33.3 | 36.8 |
| | Placebo | 2960 | 1093 | 36.9 | 35.2 | 38.7 |
| Overall/subject | HRV | 1513 | 779 | 51.5 | 48.9 | 54.0 |
| | Placebo | 1514 | 814 | 53.8 | 51.2 | 56.3 |

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

## Table 204 Percentage of doses and of subjects reporting incidence of Grade 3 AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 113 | 7.5 | 6.2 | 8.9 |
| | Placebo | 1514 | 109 | 7.2 | 5.9 | 8.6 |
| Dose 2 | HRV | 1449 | 74 | 5.1 | 4.0 | 6.4 |
| | Placebo | 1446 | 62 | 4.3 | 3.3 | 5.5 |
| Overall/dose | HRV | 2962 | 187 | 6.3 | 5.5 | 7.3 |
| | Placebo | 2960 | 171 | 5.8 | 5.0 | 6.7 |
| Overall/subject | HRV | 1513 | 170 | 11.2 | 9.7 | 12.9 |
| | Placebo | 1514 | 153 | 10.1 | 8.6 | 11.7 |

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

## Table 205 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) that are causally related to the vaccination reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 169 | 11.2 | 9.6 | 12.9 |
| | Placebo | 1514 | 150 | 9.9 | 8.4 | 11.5 |
| Dose 2 | HRV | 1449 | 113 | 7.8 | 6.5 | 9.3 |
| | Placebo | 1446 | 102 | 7.1 | 5.8 | 8.5 |
| Overall/dose | HRV | 2962 | 282 | 9.5 | 8.5 | 10.6 |
| | Placebo | 2960 | 252 | 8.5 | 7.5 | 9.6 |
| Overall/subject | HRV | 1513 | 239 | 15.8 | 14.0 | 17.7 |
| | Placebo | 1514 | 222 | 14.7 | 12.9 | 16.5 |

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

## Table 206 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) that are causally related to the vaccination reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | | General symptoms | | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| | Group | N | n | % | LL | UL |
| Dose 1 | HRV | 1513 | 204 | 13.5 | 11.8 | 15.3 |
| | Placebo | 1514 | 172 | 11.4 | 9.8 | 13.1 |
| Dose 2 | HRV | 1449 | 135 | 9.3 | 7.9 | 10.9 |
| | Placebo | 1446 | 125 | 8.6 | 7.2 | 10.2 |
| Overall/dose | HRV | 2962 | 339 | 11.4 | 10.3 | 12.6 |
| | Placebo | 2960 | 297 | 10.0 | 9.0 | 11.2 |
| Overall/subject | HRV | 1513 | 292 | 19.3 | 17.3 | 21.4 |
| | Placebo | 1514 | 259 | 17.1 | 15.2 | 19.1 |

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

## Table 207 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 65 | 42.5 | 34.5 | 50.7 | 153 | 65 | 42.5 | 34.5 | 50.7 | - | - | - | - | - |
| | Placebo | 153 | 59 | 38.6 | 30.8 | 46.8 | 153 | 59 | 38.6 | 30.8 | 46.8 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 55 | 36.7 | 29.0 | 44.9 | 150 | 45 | 30.0 | 22.8 | 38.0 | 150 | 24 | 16.0 | 10.5 | 22.9 |
| | Placebo | 151 | 55 | 36.4 | 28.8 | 44.6 | 151 | 44 | 29.1 | 22.0 | 37.1 | 151 | 18 | 11.9 | 7.2 | 18.2 |
| Overall/dose | HRV | 303 | 120 | 39.6 | 34.1 | 45.4 | 303 | 110 | 36.3 | 30.9 | 42.0 | - | - | - | - | - |
| | Placebo | 304 | 114 | 37.5 | 32.0 | 43.2 | 304 | 103 | 33.9 | 28.6 | 39.5 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 88 | 57.5 | 49.3 | 65.5 | 153 | 81 | 52.9 | 44.7 | 61.1 | - | - | - | - | - |
| | Placebo | 153 | 81 | 52.9 | 44.7 | 61.1 | 153 | 77 | 50.3 | 42.1 | 58.5 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by GSK scale Fever

## Table 208 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 67 | 43.8 | 35.8 | 52.0 | 153 | 67 | 43.8 | 35.8 | 52.0 | - | - | - | - | - |
| | Placebo | 153 | 61 | 39.9 | 32.1 | 48.1 | 153 | 61 | 39.9 | 32.1 | 48.1 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 57 | 38.0 | 30.2 | 46.3 | 150 | 47 | 31.3 | 24.0 | 39.4 | 150 | 24 | 16.0 | 10.5 | 22.9 |
| | Placebo | 151 | 59 | 39.1 | 31.2 | 47.3 | 151 | 49 | 32.5 | 25.1 | 40.5 | 151 | 18 | 11.9 | 7.2 | 18.2 |
| Overall/dose | HRV | 303 | 124 | 40.9 | 35.3 | 46.7 | 303 | 114 | 37.6 | 32.1 | 43.3 | - | - | - | - | - |
| | Placebo | 304 | 120 | 39.5 | 33.9 | 45.2 | 304 | 110 | 36.2 | 30.8 | 41.9 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 92 | 60.1 | 51.9 | 67.9 | 153 | 85 | 55.6 | 47.3 | 63.6 | - | - | - | - | - |
| | Placebo | 153 | 85 | 55.6 | 47.3 | 63.6 | 153 | 81 | 52.9 | 44.7 | 61.1 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by Chinese scale Fever

## Table 209 Percentage of doses and of subjects reporting incidence of Grade 3 AEs (solicited and unsolicited) reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 3 | 2.0 | 0.4 | 5.6 | - | - | - | - | - |
| | Placebo | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 6 | 3.9 | 1.5 | 8.3 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 6 | 4.0 | 1.5 | 8.5 | 150 | 5 | 3.3 | 1.1 | 7.6 | 150 | 2 | 1.3 | 0.2 | 4.7 |
| | Placebo | 151 | 2 | 1.3 | 0.2 | 4.7 | 151 | 1 | 0.7 | 0.0 | 3.6 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| Overall/dose | HRV | 303 | 9 | 3.0 | 1.4 | 5.6 | 303 | 8 | 2.6 | 1.1 | 5.1 | - | - | - | - | - |
| | Placebo | 304 | 8 | 2.6 | 1.1 | 5.1 | 304 | 7 | 2.3 | 0.9 | 4.7 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 8 | 5.2 | 2.3 | 10.0 | 153 | 7 | 4.6 | 1.9 | 9.2 | - | - | - | - | - |
| | Placebo | 153 | 7 | 4.6 | 1.9 | 9.2 | 153 | 6 | 3.9 | 1.5 | 8.3 | - | - | - | - | - |

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

## Table 210 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) assessed as grade 3 and are causally related to the vaccination reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 3 | 2.0 | 0.4 | 5.6 | - | - | - | - | - |
| | Placebo | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 4 | 2.7 | 0.7 | 6.7 | 150 | 2 | 1.3 | 0.2 | 4.7 | 150 | 2 | 1.3 | 0.2 | 4.7 |
| | Placebo | 151 | 2 | 1.3 | 0.2 | 4.7 | 151 | 1 | 0.7 | 0.0 | 3.6 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| Overall/dose | HRV | 303 | 7 | 2.3 | 0.9 | 4.7 | 303 | 5 | 1.7 | 0.5 | 3.8 | - | - | - | - | - |
| | Placebo | 304 | 4 | 1.3 | 0.4 | 3.3 | 304 | 3 | 1.0 | 0.2 | 2.9 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 4 | 2.6 | 0.7 | 6.6 | - | - | - | - | - |
| | Placebo | 153 | 4 | 2.6 | 0.7 | 6.6 | 153 | 3 | 2.0 | 0.4 | 5.6 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)

**Table 211 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) requiring medical attention reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 13 | 8.5 | 4.6 | 14.1 | 153 | 13 | 8.5 | 4.6 | 14.1 | - | - | - | - | - |
| | Placebo | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 12 | 7.8 | 4.1 | 13.3 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 1 | 0.7 | 0.0 | 3.7 |
| | Placebo | 151 | 5 | 3.3 | 1.1 | 7.6 | 151 | 5 | 3.3 | 1.1 | 7.6 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Overall/dose | HRV | 303 | 21 | 6.9 | 4.3 | 10.4 | 303 | 21 | 6.9 | 4.3 | 10.4 | - | - | - | - | - |
| | Placebo | 304 | 17 | 5.6 | 3.3 | 8.8 | 304 | 17 | 5.6 | 3.3 | 8.8 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 19 | 12.4 | 7.6 | 18.7 | 153 | 19 | 12.4 | 7.6 | 18.7 | - | - | - | - | - |
| | Placebo | 153 | 17 | 11.1 | 6.6 | 17.2 | 153 | 17 | 11.1 | 6.6 | 17.2 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by GSK scale Fever

**Table 212 Percentage of doses and of subjects reporting incidence of any AEs (solicited and unsolicited) requiring medical attention reported during the 8-day (Days 0- 7) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | Any symptom | | | | | General symptoms | | | | | Local symptoms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% CI | | | | | 95% CI | | | | | 95% CI | |
| | Group | N | n | % | LL | UL | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 1 | HRV | 153 | 14 | 9.2 | 5.1 | 14.9 | 153 | 14 | 9.2 | 5.1 | 14.9 | - | - | - | - | - |
| | Placebo | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 12 | 7.8 | 4.1 | 13.3 | - | - | - | - | - |
| Dose 2 | HRV | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 8 | 5.3 | 2.3 | 10.2 | 150 | 1 | 0.7 | 0.0 | 3.7 |
| | Placebo | 151 | 6 | 4.0 | 1.5 | 8.4 | 151 | 6 | 4.0 | 1.5 | 8.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Overall/dose | HRV | 303 | 22 | 7.3 | 4.6 | 10.8 | 303 | 22 | 7.3 | 4.6 | 10.8 | - | - | - | - | - |
| | Placebo | 304 | 18 | 5.9 | 3.5 | 9.2 | 304 | 18 | 5.9 | 3.5 | 9.2 | - | - | - | - | - |
| Overall/subject | HRV | 153 | 20 | 13.1 | 8.2 | 19.5 | 153 | 20 | 13.1 | 8.2 | 19.5 | - | - | - | - | - |
| | Placebo | 153 | 18 | 11.8 | 7.1 | 18.0 | 153 | 18 | 11.8 | 7.1 | 18.0 | - | - | - | - | - |

For each dose and overall/subject:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects presenting at least one type of symptom at the study vaccine site
For overall/dose:
N= number of administered doses
n/%= number/percentage of doses followed by at least one type of symptom at the study vaccine site
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Dose 1 and Dose 2 represent the dose 1 and dose 2 of study vaccines (HRV and placebo) which is same as the dose 1 and dose 2 of OPV for Immunogenicity sub-cohort 2 and dose 1 of DTPa vaccine is given along with dose 2 of study vaccines (HRV/Placebo)
Note: Tables generated by Chinese scale Fever

## 11.6.1.2. Solicited local adverse events

**Table 213 Percentage of subjects reporting each solicited local symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Dose 2 | | | | | | | | | | | |
| Pain | All | 150 | 14 | 9.3 | 5.2 | 15.2 | 151 | 9 | 6.0 | 2.8 | 11.0 |
| | Grade 3 | 150 | 2 | 1.3 | 0.2 | 4.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Redness (mm) | All | 150 | 20 | 13.3 | 8.3 | 19.8 | 151 | 13 | 8.6 | 4.7 | 14.3 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Swelling (mm) | All | 150 | 13 | 8.7 | 4.7 | 14.4 | 151 | 6 | 4.0 | 1.5 | 8.4 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |

For each dose:
N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
Dose 2 of HRV/placebo= Dose 1 of DTPa

### 11.6.1.3. Solicited general adverse events

**Table 214 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Irritability/Fussiness | All | 1666 | 369 | 22.1 | 20.2 | 24.2 | 1667 | 397 | 23.8 | 21.8 | 25.9 |
| | Grade 3 | 1666 | 28 | 1.7 | 1.1 | 2.4 | 1667 | 30 | 1.8 | 1.2 | 2.6 |
| | Related | 1666 | 128 | 7.7 | 6.4 | 9.1 | 1667 | 107 | 6.4 | 5.3 | 7.7 |
| | Grade 3 Related | 1666 | 13 | 0.8 | 0.4 | 1.3 | 1667 | 12 | 0.7 | 0.4 | 1.3 |
| Loss of appetite | All | 1666 | 209 | 12.5 | 11.0 | 14.2 | 1667 | 209 | 12.5 | 11.0 | 14.2 |
| | Grade 3 | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 5 | 0.3 | 0.1 | 0.7 |
| | Related | 1666 | 76 | 4.6 | 3.6 | 5.7 | 1667 | 60 | 3.6 | 2.8 | 4.6 |
| | Grade 3 Related | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| Temperature/ (Axillary) (°C) according Chinese scale | All | 1666 | 211 | 12.7 | 11.1 | 14.4 | 1667 | 223 | 13.4 | 11.8 | 15.1 |
| | Grade 3 | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| | Related | 1666 | 74 | 4.4 | 3.5 | 5.5 | 1667 | 59 | 3.5 | 2.7 | 4.5 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Temperature/ (Axillary) (°C) according GSK scale | All | 1666 | 44 | 2.6 | 1.9 | 3.5 | 1667 | 68 | 4.1 | 3.2 | 5.1 |
| | Grade 3 | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| | Related | 1666 | 19 | 1.1 | 0.7 | 1.8 | 1667 | 16 | 1.0 | 0.5 | 1.6 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| **Dose 2** | | | | | | | | | | | |
| Irritability/Fussiness | All | 1599 | 215 | 13.4 | 11.8 | 15.2 | 1597 | 233 | 14.6 | 12.9 | 16.4 |
| | Grade 3 | 1599 | 23 | 1.4 | 0.9 | 2.2 | 1597 | 18 | 1.1 | 0.7 | 1.8 |
| | Related | 1599 | 81 | 5.1 | 4.0 | 6.3 | 1597 | 66 | 4.1 | 3.2 | 5.2 |
| | Grade 3 Related | 1599 | 10 | 0.6 | 0.3 | 1.1 | 1597 | 9 | 0.6 | 0.3 | 1.1 |
| Loss of appetite | All | 1599 | 139 | 8.7 | 7.4 | 10.2 | 1597 | 133 | 8.3 | 7.0 | 9.8 |
| | Grade 3 | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 4 | 0.3 | 0.1 | 0.6 |
| | Related | 1599 | 48 | 3.0 | 2.2 | 4.0 | 1597 | 39 | 2.4 | 1.7 | 3.3 |
| | Grade 3 Related | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 3 | 0.2 | 0.0 | 0.5 |
| Temperature/ (Axillary) (°C) according Chinese scale | All | 1599 | 152 | 9.5 | 8.1 | 11.1 | 1597 | 151 | 9.5 | 8.1 | 11.0 |
| | Grade 3 | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| | Related | 1599 | 42 | 2.6 | 1.9 | 3.5 | 1597 | 40 | 2.5 | 1.8 | 3.4 |
| | Grade 3 Related | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| Temperature/ (Axillary) (°C) according GSK scale | All | 1599 | 49 | 3.1 | 2.3 | 4.0 | 1597 | 47 | 2.9 | 2.2 | 3.9 |
| | Grade 3 | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| | Related | 1599 | 8 | 0.5 | 0.2 | 1.0 | 1597 | 11 | 0.7 | 0.3 | 1.2 |
| | Grade 3 Related | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 1 | 0.1 | 0.0 | 0.3 |

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

**Table 215 Percentage of doses and subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Overall/dose** | | | | | | | | | | | |
| Irritability/Fussiness | All | 3265 | 584 | 17.9 | 16.6 | 19.2 | 3264 | 630 | 19.3 | 18.0 | 20.7 |
| | Grade 3 | 3265 | 51 | 1.6 | 1.2 | 2.0 | 3264 | 48 | 1.5 | 1.1 | 1.9 |
| | Related | 3265 | 209 | 6.4 | 5.6 | 7.3 | 3264 | 173 | 5.3 | 4.6 | 6.1 |
| | Grade 3 Related | 3265 | 23 | 0.7 | 0.4 | 1.1 | 3264 | 21 | 0.6 | 0.4 | 1.0 |
| Loss of appetite | All | 3265 | 348 | 10.7 | 9.6 | 11.8 | 3264 | 342 | 10.5 | 9.4 | 11.6 |
| | Grade 3 | 3265 | 5 | 0.2 | 0.0 | 0.4 | 3264 | 9 | 0.3 | 0.1 | 0.5 |
| | Related | 3265 | 124 | 3.8 | 3.2 | 4.5 | 3264 | 99 | 3.0 | 2.5 | 3.7 |
| | Grade 3 Related | 3265 | 4 | 0.1 | 0.0 | 0.3 | 3264 | 5 | 0.2 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 3265 | 363 | 11.1 | 10.1 | 12.2 | 3264 | 374 | 11.5 | 10.4 | 12.6 |
| | Grade 3 | 3265 | 1 | 0.0 | 0.0 | 0.2 | 3264 | 3 | 0.1 | 0.0 | 0.3 |
| | Related | 3265 | 116 | 3.6 | 2.9 | 4.2 | 3264 | 99 | 3.0 | 2.5 | 3.7 |
| | Grade 3 Related | 3265 | 0 | 0.0 | 0.0 | 0.1 | 3264 | 1 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 3265 | 93 | 2.8 | 2.3 | 3.5 | 3264 | 115 | 3.5 | 2.9 | 4.2 |
| | Grade 3 | 3265 | 1 | 0.0 | 0.0 | 0.2 | 3264 | 3 | 0.1 | 0.0 | 0.3 |
| | Related | 3265 | 27 | 0.8 | 0.5 | 1.2 | 3264 | 27 | 0.8 | 0.5 | 1.2 |
| | Grade 3 Related | 3265 | 0 | 0.0 | 0.0 | 0.1 | 3264 | 1 | 0.0 | 0.0 | 0.2 |
| **Overall/subject** | | | | | | | | | | | |
| Irritability/Fussiness | All | 1666 | 471 | 28.3 | 26.1 | 30.5 | 1667 | 500 | 30.0 | 27.8 | 32.3 |
| | Grade 3 | 1666 | 48 | 2.9 | 2.1 | 3.8 | 1667 | 43 | 2.6 | 1.9 | 3.5 |
| | Related | 1666 | 176 | 10.6 | 9.1 | 12.1 | 1667 | 154 | 9.2 | 7.9 | 10.7 |
| | Grade 3 Related | 1666 | 20 | 1.2 | 0.7 | 1.8 | 1667 | 20 | 1.2 | 0.7 | 1.8 |
| Loss of appetite | All | 1666 | 296 | 17.8 | 16.0 | 19.7 | 1667 | 282 | 16.9 | 15.1 | 18.8 |
| | Grade 3 | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 9 | 0.5 | 0.2 | 1.0 |
| | Related | 1666 | 107 | 6.4 | 5.3 | 7.7 | 1667 | 90 | 5.4 | 4.4 | 6.6 |
| | Grade 3 Related | 1666 | 4 | 0.2 | 0.1 | 0.6 | 1667 | 5 | 0.3 | 0.1 | 0.7 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1666 | 320 | 19.2 | 17.3 | 21.2 | 1667 | 333 | 20.0 | 18.1 | 22.0 |
| | Grade 3 | 1666 | 1 | 0.1 | 0.0 | 0.3 | 1667 | 3 | 0.2 | 0.0 | 0.5 |
| | Related | 1666 | 112 | 6.7 | 5.6 | 8.0 | 1667 | 96 | 5.8 | 4.7 | 7.0 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 1 | 0.1 | 0.0 | 0.3 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1666 | 89 | 5.3 | 4.3 | 6.5 | 1667 | 111 | 6.7 | 5.5 | 8.0 |
| | Grade 3 | 1666 | 1 | 0.1 | 0.0 | 0.3 | 1667 | 3 | 0.2 | 0.0 | 0.5 |
| | Related | 1666 | 27 | 1.6 | 1.1 | 2.3 | 1667 | 27 | 1.6 | 1.1 | 2.3 |
| | Grade 3 Related | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 1 | 0.1 | 0.0 | 0.3 |

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

## Table 216 Percentage of subjects reporting fever during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort)

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 1666 | 211 | 12.7 | 11.1 | 14.4 | 1667 | 223 | 13.4 | 11.8 | 15.1 |
| | >37.0°C | 1666 | 211 | 12.7 | 11.1 | 14.4 | 1667 | 223 | 13.4 | 11.8 | 15.1 |
| | >37.5°C | 1666 | 32 | 1.9 | 1.3 | 2.7 | 1667 | 52 | 3.1 | 2.3 | 4.1 |
| | >38.0°C | 1666 | 11 | 0.7 | 0.3 | 1.2 | 1667 | 21 | 1.3 | 0.8 | 1.9 |
| | >38.5°C | 1666 | 6 | 0.4 | 0.1 | 0.8 | 1667 | 10 | 0.6 | 0.3 | 1.1 |
| | >39.0°C | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 2 | 0.1 | 0.0 | 0.4 |
| **Dose 2** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 1599 | 152 | 9.5 | 8.1 | 11.1 | 1597 | 151 | 9.5 | 8.1 | 11.0 |
| | >37.0°C | 1599 | 152 | 9.5 | 8.1 | 11.1 | 1597 | 151 | 9.5 | 8.1 | 11.0 |
| | >37.5°C | 1599 | 40 | 2.5 | 1.8 | 3.4 | 1597 | 35 | 2.2 | 1.5 | 3.0 |
| | >38.0°C | 1599 | 17 | 1.1 | 0.6 | 1.7 | 1597 | 14 | 0.9 | 0.5 | 1.5 |
| | >38.5°C | 1599 | 5 | 0.3 | 0.1 | 0.7 | 1597 | 7 | 0.4 | 0.2 | 0.9 |
| | >39.0°C | 1599 | 1 | 0.1 | 0.0 | 0.3 | 1597 | 1 | 0.1 | 0.0 | 0.3 |
| **Overall/dose** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 3265 | 363 | 11.1 | 10.1 | 12.2 | 3264 | 374 | 11.5 | 10.4 | 12.6 |
| | >37.0°C | 3265 | 363 | 11.1 | 10.1 | 12.2 | 3264 | 374 | 11.5 | 10.4 | 12.6 |
| | >37.5°C | 3265 | 72 | 2.2 | 1.7 | 2.8 | 3264 | 87 | 2.7 | 2.1 | 3.3 |
| | >38.0°C | 3265 | 28 | 0.9 | 0.6 | 1.2 | 3264 | 35 | 1.1 | 0.7 | 1.5 |
| | >38.5°C | 3265 | 11 | 0.3 | 0.2 | 0.6 | 3264 | 17 | 0.5 | 0.3 | 0.8 |
| | >39.0°C | 3265 | 1 | 0.0 | 0.0 | 0.2 | 3264 | 3 | 0.1 | 0.0 | 0.3 |
| **Overall/subject** | | | | | | | | | | | |
| Temperature/(Axillary) (°C) | All | 1666 | 320 | 19.2 | 17.3 | 21.2 | 1667 | 333 | 20.0 | 18.1 | 22.0 |
| | >37.0°C | 1666 | 320 | 19.2 | 17.3 | 21.2 | 1667 | 333 | 20.0 | 18.1 | 22.0 |
| | >37.5°C | 1666 | 71 | 4.3 | 3.3 | 5.3 | 1667 | 84 | 5.0 | 4.0 | 6.2 |
| | >38.0°C | 1666 | 28 | 1.7 | 1.1 | 2.4 | 1667 | 34 | 2.0 | 1.4 | 2.8 |
| | >38.5°C | 1666 | 11 | 0.7 | 0.3 | 1.2 | 1667 | 17 | 1.0 | 0.6 | 1.6 |
| | >39.0°C | 1666 | 1 | 0.1 | 0.0 | 0.3 | 1667 | 3 | 0.2 | 0.0 | 0.5 |

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

**Table 217 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Cough/runny nose | All | 1513 | 191 | 12.6 | 11.0 | 14.4 | 1514 | 221 | 14.6 | 12.9 | 16.5 |
| | Grade 3 | 1513 | 9 | 0.6 | 0.3 | 1.1 | 1514 | 4 | 0.3 | 0.1 | 0.7 |
| | Related | 1513 | 38 | 2.5 | 1.8 | 3.4 | 1514 | 30 | 2.0 | 1.3 | 2.8 |
| | Grade 3 Related | 1513 | 5 | 0.3 | 0.1 | 0.8 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Diarrhoea | All | 1513 | 80 | 5.3 | 4.2 | 6.5 | 1514 | 87 | 5.7 | 4.6 | 7.0 |
| | Grade 3 | 1513 | 31 | 2.0 | 1.4 | 2.9 | 1514 | 45 | 3.0 | 2.2 | 4.0 |
| | Related | 1513 | 38 | 2.5 | 1.8 | 3.4 | 1514 | 36 | 2.4 | 1.7 | 3.3 |
| | Grade 3 Related | 1513 | 17 | 1.1 | 0.7 | 1.8 | 1514 | 22 | 1.5 | 0.9 | 2.2 |
| Irritability/Fussiness | All | 1513 | 325 | 21.5 | 19.4 | 23.6 | 1514 | 357 | 23.6 | 21.5 | 25.8 |
| | Grade 3 | 1513 | 26 | 1.7 | 1.1 | 2.5 | 1514 | 26 | 1.7 | 1.1 | 2.5 |
| | Related | 1513 | 113 | 7.5 | 6.2 | 8.9 | 1514 | 102 | 6.7 | 5.5 | 8.1 |
| | Grade 3 Related | 1513 | 11 | 0.7 | 0.4 | 1.3 | 1514 | 11 | 0.7 | 0.4 | 1.3 |
| Loss of appetite | All | 1513 | 178 | 11.8 | 10.2 | 13.5 | 1514 | 186 | 12.3 | 10.7 | 14.0 |
| | Grade 3 | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 3 | 0.2 | 0.0 | 0.6 |
| | Related | 1513 | 63 | 4.2 | 3.2 | 5.3 | 1514 | 58 | 3.8 | 2.9 | 4.9 |
| | Grade 3 Related | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 2 | 0.1 | 0.0 | 0.5 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1513 | 199 | 13.2 | 11.5 | 15.0 | 1514 | 213 | 14.1 | 12.4 | 15.9 |
| | Grade 3 | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1513 | 66 | 4.4 | 3.4 | 5.5 | 1514 | 55 | 3.6 | 2.7 | 4.7 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1513 | 41 | 2.7 | 2.0 | 3.7 | 1514 | 66 | 4.4 | 3.4 | 5.5 |
| | Grade 3 | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1513 | 17 | 1.1 | 0.7 | 1.8 | 1514 | 15 | 1.0 | 0.6 | 1.6 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Vomiting | All | 1513 | 165 | 10.9 | 9.4 | 12.6 | 1514 | 176 | 11.6 | 10.1 | 13.3 |
| | Grade 3 | 1513 | 59 | 3.9 | 3.0 | 5.0 | 1514 | 56 | 3.7 | 2.8 | 4.8 |
| | Related | 1513 | 38 | 2.5 | 1.8 | 3.4 | 1514 | 26 | 1.7 | 1.1 | 2.5 |
| | Grade 3 Related | 1513 | 16 | 1.1 | 0.6 | 1.7 | 1514 | 13 | 0.9 | 0.5 | 1.5 |
| **Dose 2** | | | | | | | | | | | |
| Cough/runny nose | All | 1449 | 191 | 13.2 | 11.5 | 15.0 | 1446 | 214 | 14.8 | 13.0 | 16.7 |
| | Grade 3 | 1449 | 11 | 0.8 | 0.4 | 1.4 | 1446 | 3 | 0.2 | 0.0 | 0.6 |
| | Related | 1449 | 32 | 2.2 | 1.5 | 3.1 | 1446 | 36 | 2.5 | 1.7 | 3.4 |
| | Grade 3 Related | 1449 | 2 | 0.1 | 0.0 | 0.5 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| Diarrhoea | All | 1449 | 57 | 3.9 | 3.0 | 5.1 | 1446 | 45 | 3.1 | 2.3 | 4.1 |
| | Grade 3 | 1449 | 25 | 1.7 | 1.1 | 2.5 | 1446 | 18 | 1.2 | 0.7 | 2.0 |
| | Related | 1449 | 22 | 1.5 | 1.0 | 2.3 | 1446 | 15 | 1.0 | 0.6 | 1.7 |
| | Grade 3 Related | 1449 | 10 | 0.7 | 0.3 | 1.3 | 1446 | 8 | 0.6 | 0.2 | 1.1 |
| Irritability/Fussiness | All | 1449 | 187 | 12.9 | 11.2 | 14.7 | 1446 | 207 | 14.3 | 12.5 | 16.2 |
| | Grade 3 | 1449 | 19 | 1.3 | 0.8 | 2.0 | 1446 | 17 | 1.2 | 0.7 | 1.9 |
| | Related | 1449 | 72 | 5.0 | 3.9 | 6.2 | 1446 | 61 | 4.2 | 3.2 | 5.4 |
| | Grade 3 Related | 1449 | 9 | 0.6 | 0.3 | 1.2 | 1446 | 8 | 0.6 | 0.2 | 1.1 |
| Loss of appetite | All | 1449 | 118 | 8.1 | 6.8 | 9.7 | 1446 | 117 | 8.1 | 6.7 | 9.6 |
| | Grade 3 | 1449 | 1 | 0.1 | 0.0 | 0.4 | 1446 | 4 | 0.3 | 0.1 | 0.7 |
| | Related | 1449 | 39 | 2.7 | 1.9 | 3.7 | 1446 | 34 | 2.4 | 1.6 | 3.3 |
| | Grade 3 Related | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 3 | 0.2 | 0.0 | 0.6 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1449 | 144 | 9.9 | 8.4 | 11.6 | 1446 | 139 | 9.6 | 8.1 | 11.2 |
| | Grade 3 | 1449 | 1 | 0.1 | 0.0 | 0.4 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1449 | 39 | 2.7 | 1.9 | 3.7 | 1446 | 39 | 2.7 | 1.9 | 3.7 |
| | Grade 3 Related | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1449 | 46 | 3.2 | 2.3 | 4.2 | 1446 | 42 | 2.9 | 2.1 | 3.9 |
| | Grade 3 | 1449 | 1 | 0.1 | 0.0 | 0.4 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| | Related | 1449 | 7 | 0.5 | 0.2 | 1.0 | 1446 | 11 | 0.8 | 0.4 | 1.4 |
| | Grade 3 Related | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 1 | 0.1 | 0.0 | 0.4 |
| Vomiting | All | 1449 | 91 | 6.3 | 5.1 | 7.7 | 1446 | 100 | 6.9 | 5.7 | 8.3 |
| | Grade 3 | 1449 | 30 | 2.1 | 1.4 | 2.9 | 1446 | 29 | 2.0 | 1.3 | 2.9 |
| | Related | 1449 | 26 | 1.8 | 1.2 | 2.6 | 1446 | 12 | 0.8 | 0.4 | 1.4 |
| | Grade 3 Related | 1449 | 10 | 0.7 | 0.3 | 1.3 | 1446 | 4 | 0.3 | 0.1 | 0.7 |

N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once

**Table 218 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Overall/dose** | | | | | | | | | | | |
| Cough/runny nose | All | 2962 | 382 | 12.9 | 11.7 | 14.2 | 2960 | 435 | 14.7 | 13.4 | 16.0 |
| | Grade 3 | 2962 | 20 | 0.7 | 0.4 | 1.0 | 2960 | 7 | 0.2 | 0.1 | 0.5 |
| | Related | 2962 | 70 | 2.4 | 1.8 | 3.0 | 2960 | 66 | 2.2 | 1.7 | 2.8 |
| | Grade 3 Related | 2962 | 7 | 0.2 | 0.1 | 0.5 | 2960 | 1 | 0.0 | 0.0 | 0.2 |
| Diarrhoea | All | 2962 | 137 | 4.6 | 3.9 | 5.4 | 2960 | 132 | 4.5 | 3.7 | 5.3 |
| | Grade 3 | 2962 | 56 | 1.9 | 1.4 | 2.4 | 2960 | 63 | 2.1 | 1.6 | 2.7 |
| | Related | 2962 | 60 | 2.0 | 1.5 | 2.6 | 2960 | 51 | 1.7 | 1.3 | 2.3 |
| | Grade 3 Related | 2962 | 27 | 0.9 | 0.6 | 1.3 | 2960 | 30 | 1.0 | 0.7 | 1.4 |
| Irritability/Fussiness | All | 2962 | 512 | 17.3 | 15.9 | 18.7 | 2960 | 564 | 19.1 | 17.7 | 20.5 |
| | Grade 3 | 2962 | 45 | 1.5 | 1.1 | 2.0 | 2960 | 43 | 1.5 | 1.1 | 2.0 |
| | Related | 2962 | 185 | 6.2 | 5.4 | 7.2 | 2960 | 163 | 5.5 | 4.7 | 6.4 |
| | Grade 3 Related | 2962 | 20 | 0.7 | 0.4 | 1.0 | 2960 | 19 | 0.6 | 0.4 | 1.0 |
| Loss of appetite | All | 2962 | 296 | 10.0 | 8.9 | 11.1 | 2960 | 303 | 10.2 | 9.2 | 11.4 |
| | Grade 3 | 2962 | 4 | 0.1 | 0.0 | 0.3 | 2960 | 7 | 0.2 | 0.1 | 0.5 |
| | Related | 2962 | 102 | 3.4 | 2.8 | 4.2 | 2960 | 92 | 3.1 | 2.5 | 3.8 |
| | Grade 3 Related | 2962 | 3 | 0.1 | 0.0 | 0.3 | 2960 | 5 | 0.2 | 0.1 | 0.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 2962 | 343 | 11.5 | 10.4 | 12.8 | 2960 | 352 | 11.9 | 10.7 | 13.1 |
| | Grade 3 | 2962 | 1 | 0.0 | 0.0 | 0.2 | 2960 | 2 | 0.1 | 0.0 | 0.2 |
| | Related | 2962 | 105 | 3.5 | 2.9 | 4.3 | 2960 | 94 | 3.2 | 2.6 | 3.9 |
| | Grade 3 Related | 2962 | 0 | 0.0 | 0.0 | 0.1 | 2960 | 1 | 0.0 | 0.0 | 0.2 |
| Temperature/(Axillary) (°C) according GSK scale | All | 2962 | 87 | 2.9 | 2.4 | 3.6 | 2960 | 108 | 3.6 | 3.0 | 4.4 |
| | Grade 3 | 2962 | 1 | 0.0 | 0.0 | 0.2 | 2960 | 2 | 0.1 | 0.0 | 0.2 |
| | Related | 2962 | 24 | 0.8 | 0.5 | 1.2 | 2960 | 26 | 0.9 | 0.6 | 1.3 |
| | Grade 3 Related | 2962 | 0 | 0.0 | 0.0 | 0.1 | 2960 | 1 | 0.0 | 0.0 | 0.2 |
| Vomiting | All | 2962 | 256 | 8.6 | 7.7 | 9.7 | 2960 | 276 | 9.3 | 8.3 | 10.4 |
| | Grade 3 | 2962 | 89 | 3.0 | 2.4 | 3.7 | 2960 | 85 | 2.9 | 2.3 | 3.5 |
| | Related | 2962 | 64 | 2.2 | 1.7 | 2.8 | 2960 | 38 | 1.3 | 0.9 | 1.8 |
| | Grade 3 Related | 2962 | 26 | 0.9 | 0.6 | 1.3 | 2960 | 17 | 0.6 | 0.3 | 0.9 |
| **Overall/subject** | | | | | | | | | | | |
| Cough/runny nose | All | 1513 | 313 | 20.7 | 18.7 | 22.8 | 1514 | 366 | 24.2 | 22.0 | 26.4 |
| | Grade 3 | 1513 | 19 | 1.3 | 0.8 | 2.0 | 1514 | 7 | 0.5 | 0.2 | 1.0 |
| | Related | 1513 | 64 | 4.2 | 3.3 | 5.4 | 1514 | 58 | 3.8 | 2.9 | 4.9 |
| | Grade 3 Related | 1513 | 7 | 0.5 | 0.2 | 1.0 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| Diarrhoea | All | 1513 | 127 | 8.4 | 7.0 | 9.9 | 1514 | 123 | 8.1 | 6.8 | 9.6 |
| | Grade 3 | 1513 | 55 | 3.6 | 2.8 | 4.7 | 1514 | 60 | 4.0 | 3.0 | 5.1 |
| | Related | 1513 | 58 | 3.8 | 2.9 | 4.9 | 1514 | 49 | 3.2 | 2.4 | 4.3 |
| | Grade 3 Related | 1513 | 26 | 1.7 | 1.1 | 2.5 | 1514 | 29 | 1.9 | 1.3 | 2.7 |
| Irritability/Fussiness | All | 1513 | 415 | 27.4 | 25.2 | 29.8 | 1514 | 448 | 29.6 | 27.3 | 32.0 |
| | Grade 3 | 1513 | 43 | 2.8 | 2.1 | 3.8 | 1514 | 39 | 2.6 | 1.8 | 3.5 |
| | Related | 1513 | 158 | 10.4 | 8.9 | 12.1 | 1514 | 144 | 9.5 | 8.1 | 11.1 |
| | Grade 3 Related | 1513 | 18 | 1.2 | 0.7 | 1.9 | 1514 | 18 | 1.2 | 0.7 | 1.9 |
| Loss of appetite | All | 1513 | 253 | 16.7 | 14.9 | 18.7 | 1514 | 250 | 16.5 | 14.7 | 18.5 |
| | Grade 3 | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 7 | 0.5 | 0.2 | 1.0 |
| | Related | 1513 | 90 | 5.9 | 4.8 | 7.3 | 1514 | 83 | 5.5 | 4.4 | 6.8 |
| | Grade 3 Related | 1513 | 3 | 0.2 | 0.0 | 0.6 | 1514 | 5 | 0.3 | 0.1 | 0.8 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Temperature/(Axillary) (°C) according Chinese scale | All | 1513 | 302 | 20.0 | 18.0 | 22.1 | 1514 | 313 | 20.7 | 18.7 | 22.8 |
| | Grade 3 | 1513 | 1 | 0.1 | 0.0 | 0.4 | 1514 | 2 | 0.1 | 0.0 | 0.5 |
| | Related | 1513 | 101 | 6.7 | 5.5 | 8.1 | 1514 | 91 | 6.0 | 4.9 | 7.3 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| Temperature/(Axillary) (°C) according GSK scale | All | 1513 | 83 | 5.5 | 4.4 | 6.8 | 1514 | 104 | 6.9 | 5.6 | 8.3 |
| | Grade 3 | 1513 | 1 | 0.1 | 0.0 | 0.4 | 1514 | 2 | 0.1 | 0.0 | 0.5 |
| | Related | 1513 | 24 | 1.6 | 1.0 | 2.4 | 1514 | 26 | 1.7 | 1.1 | 2.5 |
| | Grade 3 Related | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 1 | 0.1 | 0.0 | 0.4 |
| Vomiting | All | 1513 | 213 | 14.1 | 12.4 | 15.9 | 1514 | 232 | 15.3 | 13.5 | 17.2 |
| | Grade 3 | 1513 | 80 | 5.3 | 4.2 | 6.5 | 1514 | 75 | 5.0 | 3.9 | 6.2 |
| | Related | 1513 | 57 | 3.8 | 2.9 | 4.9 | 1514 | 33 | 2.2 | 1.5 | 3.0 |
| | Grade 3 Related | 1513 | 23 | 1.5 | 1.0 | 2.3 | 1514 | 16 | 1.1 | 0.6 | 1.7 |

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

**Table 219 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | | |
| Drowsiness | All | 153 | 37 | 24.2 | 17.6 | 31.8 | 153 | 26 | 17.0 | 11.4 | 23.9 |
| | Grade 3 | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 9 | 5.9 | 2.7 | 10.9 | 153 | 6 | 3.9 | 1.5 | 8.3 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Gastrointestinal | All | 153 | 36 | 23.5 | 17.1 | 31.1 | 153 | 31 | 20.3 | 14.2 | 27.5 |
| | Grade 3 | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 14 | 9.2 | 5.1 | 14.9 | 153 | 9 | 5.9 | 2.7 | 10.9 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 5 | 3.3 | 1.1 | 7.5 |
| Irritability/Fussiness | All | 153 | 44 | 28.8 | 21.7 | 36.6 | 153 | 40 | 26.1 | 19.4 | 33.9 |
| | Grade 3 | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 4 | 2.6 | 0.7 | 6.6 |
| | Related | 153 | 15 | 9.8 | 5.6 | 15.7 | 153 | 5 | 3.3 | 1.1 | 7.5 |
| | Grade 3 Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 3 | 2.0 | 0.4 | 5.6 |
| Loss of appetite | All | 153 | 31 | 20.3 | 14.2 | 27.5 | 153 | 23 | 15.0 | 9.8 | 21.7 |
| | Grade 3 | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 13 | 8.5 | 4.6 | 14.1 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 10 | 6.5 | 3.2 | 11.7 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 8 | 5.2 | 2.3 | 10.0 | 153 | 4 | 2.6 | 0.7 | 6.6 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| Temperature/(Axillary) (°C) according GSK scale | All | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| **Dose 2** | | | | | | | | | | | |
| Drowsiness | All | 150 | 21 | 14.0 | 8.9 | 20.6 | 151 | 23 | 15.2 | 9.9 | 22.0 |
| | Grade 3 | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 6 | 4.0 | 1.5 | 8.5 | 151 | 7 | 4.6 | 1.9 | 9.3 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Gastrointestinal | All | 150 | 20 | 13.3 | 8.3 | 19.8 | 151 | 18 | 11.9 | 7.2 | 18.2 |
| | Grade 3 | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 6 | 4.0 | 1.5 | 8.5 | 151 | 7 | 4.6 | 1.9 | 9.3 |
| | Grade 3 Related | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Irritability/Fussiness | All | 150 | 28 | 18.7 | 12.8 | 25.8 | 151 | 26 | 17.2 | 11.6 | 24.2 |
| | Grade 3 | 150 | 4 | 2.7 | 0.7 | 6.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 150 | 9 | 6.0 | 2.8 | 11.1 | 151 | 5 | 3.3 | 1.1 | 7.6 |
| | Grade 3 Related | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| **Symptom** | **Type** | **N** | **n** | **%** | **LL** | **UL** | **N** | **n** | **%** | **LL** | **UL** |
| Loss of appetite | All | 150 | 21 | 14.0 | 8.9 | 20.6 | 151 | 16 | 10.6 | 6.2 | 16.6 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 9 | 6.0 | 2.8 | 11.1 | 151 | 5 | 3.3 | 1.1 | 7.6 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Temperature/(Axillary) (°C) according Chinese scale | All | 150 | 8 | 5.3 | 2.3 | 10.2 | 151 | 12 | 7.9 | 4.2 | 13.5 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 3 | 2.0 | 0.4 | 5.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 1 | 0.7 | 0.0 | 3.6 |
| Temperature/(Axillary) (°C) accordingGSK scale | All | 150 | 3 | 2.0 | 0.4 | 5.7 | 151 | 5 | 3.3 | 1.1 | 7.6 |
| | Grade 3 | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Related | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Grade 3 Related | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 150 | 1 | 0.7 | 0.0 | 3.7 | 151 | 0 | 0.0 | 0.0 | 2.4 |

N= number of subjects with at least one administered dose
n/%= number/percentage of subjects reporting the symptom at least once

**Table 220 Percentage of subjects reporting each solicited general symptom including those grade 3 in intensity and those assessed as related to vaccination during the 8-day (Days 0- 7) solicited follow-up period, for all doses and per subject (Total vaccinated cohort-Immunogenicity sub-cohort 2)**

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Overall/dose | | | | | | | | | | | |
| Drowsiness | All | 303 | 58 | 19.1 | 14.9 | 24.0 | 304 | 49 | 16.1 | 12.2 | 20.7 |
| | Grade 3 | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Related | 303 | 15 | 5.0 | 2.8 | 8.0 | 304 | 13 | 4.3 | 2.3 | 7.2 |
| | Grade 3 Related | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Gastrointestinal | All | 303 | 56 | 18.5 | 14.3 | 23.3 | 304 | 49 | 16.1 | 12.2 | 20.7 |
| | Grade 3 | 303 | 2 | 0.7 | 0.1 | 2.4 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| | Related | 303 | 20 | 6.6 | 4.1 | 10.0 | 304 | 16 | 5.3 | 3.0 | 8.4 |
| | Grade 3 Related | 303 | 2 | 0.7 | 0.1 | 2.4 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Medical attention | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 5 | 1.6 | 0.5 | 3.8 |
| Irritability/ Fussiness | All | 303 | 72 | 23.8 | 19.1 | 29.0 | 304 | 66 | 21.7 | 17.2 | 26.8 |
| | Grade 3 | 303 | 6 | 2.0 | 0.7 | 4.3 | 304 | 5 | 1.6 | 0.5 | 3.8 |
| | Related | 303 | 24 | 7.9 | 5.1 | 11.6 | 304 | 10 | 3.3 | 1.6 | 6.0 |
| | Grade 3 Related | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| | Medical attention | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 3 | 1.0 | 0.2 | 2.9 |
| Loss of appetite | All | 303 | 52 | 17.2 | 13.1 | 21.9 | 304 | 39 | 12.8 | 9.3 | 17.1 |
| | Grade 3 | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| | Related | 303 | 22 | 7.3 | 4.6 | 10.8 | 304 | 7 | 2.3 | 0.9 | 4.7 |
| | Grade 3 Related | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 2 | 0.7 | 0.1 | 2.4 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Temperature/ (Axillary) (°C) according Chinese scale | All | 303 | 20 | 6.6 | 4.1 | 10.0 | 304 | 22 | 7.2 | 4.6 | 10.8 |
| | Grade 3 | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Related | 303 | 11 | 3.6 | 1.8 | 6.4 | 304 | 5 | 1.6 | 0.5 | 3.8 |
| | Grade 3 Related | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Temperature/ (Axillary) (°C) according GSK scale | All | 303 | 6 | 2.0 | 0.7 | 4.3 | 304 | 7 | 2.3 | 0.9 | 4.7 |
| | Grade 3 | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Related | 303 | 3 | 1.0 | 0.2 | 2.9 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | Grade 3 Related | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| | Medical attention | 303 | 1 | 0.3 | 0.0 | 1.8 | 304 | 1 | 0.3 | 0.0 | 1.8 |
| | | | | | | | | | | | |
| Overall/subject | | | | | | | | | | | |
| Drowsiness | All | 153 | 44 | 28.8 | 21.7 | 36.6 | 153 | 38 | 24.8 | 18.2 | 32.5 |
| | Grade 3 | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 12 | 7.8 | 4.1 | 13.3 | 153 | 11 | 7.2 | 3.6 | 12.5 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Gastrointestinal | All | 153 | 43 | 28.1 | 21.1 | 35.9 | 153 | 38 | 24.8 | 18.2 | 32.5 |
| | Grade 3 | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 17 | 11.1 | 6.6 | 17.2 | 153 | 15 | 9.8 | 5.6 | 15.7 |
| | Grade 3 Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Medical attention | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 5 | 3.3 | 1.1 | 7.5 |

| | | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95 % CI | | | | | 95 % CI | |
| Symptom | Type | N | n | % | LL | UL | N | n | % | LL | UL |
| Irritability/ Fussiness | All | 153 | 56 | 36.6 | 29.0 | 44.8 | 153 | 52 | 34.0 | 26.5 | 42.1 |
| | Grade 3 | 153 | 5 | 3.3 | 1.1 | 7.5 | 153 | 4 | 2.6 | 0.7 | 6.6 |
| | Related | 153 | 18 | 11.8 | 7.1 | 18.0 | 153 | 10 | 6.5 | 3.2 | 11.7 |
| | Grade 3 Related | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 3 | 2.0 | 0.4 | 5.6 |
| Loss of appetite | All | 153 | 43 | 28.1 | 21.1 | 35.9 | 153 | 32 | 20.9 | 14.8 | 28.2 |
| | Grade 3 | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| | Related | 153 | 17 | 11.1 | 6.6 | 17.2 | 153 | 7 | 4.6 | 1.9 | 9.2 |
| | Grade 3 Related | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 2 | 1.3 | 0.2 | 4.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Temperature/ (Axillary) (°C) according Chinese scale | All | 153 | 18 | 11.8 | 7.1 | 18.0 | 153 | 20 | 13.1 | 8.2 | 19.5 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 11 | 7.2 | 3.6 | 12.5 | 153 | 5 | 3.3 | 1.1 | 7.5 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Temperature/ (Axillary) (°C) according GSK scale | All | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 7 | 4.6 | 1.9 | 9.2 |
| | Grade 3 | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Related | 153 | 3 | 2.0 | 0.4 | 5.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |
| | Grade 3 Related | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| | Medical attention | 153 | 1 | 0.7 | 0.0 | 3.6 | 153 | 1 | 0.7 | 0.0 | 3.6 |

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

### 11.6.1.4. Unsolicited adverse events

**Table 221 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)**

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 310 | 18.6 | 16.8 | 20.6 | 368 | 22.1 | 20.1 | 24.1 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Heart disease congenital (10019273) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Hydrocele (10020488) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Thalassaemia (10043388) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Abdominal pain (10000081) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Constipation (10010774) | 15 | 0.9 | 0.5 | 1.5 | 9 | 0.5 | 0.2 | 1.0 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.4 | 6 | 0.4 | 0.1 | 0.8 |
| | Dyspepsia (10013946) | 8 | 0.5 | 0.2 | 0.9 | 7 | 0.4 | 0.2 | 0.9 |
| | Enteritis (10014866) | 6 | 0.4 | 0.1 | 0.8 | 14 | 0.8 | 0.5 | 1.4 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Mouth ulceration (10028034) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Vomiting (10047700) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Pyrexia (10037660) | 13 | 0.8 | 0.4 | 1.3 | 27 | 1.6 | 1.1 | 2.3 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hypersensitivity (10020751) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchitis (10006451) | 18 | 1.1 | 0.6 | 1.7 | 27 | 1.6 | 1.1 | 2.3 |
| | Bronchopneumonia (10006469) | 9 | 0.5 | 0.2 | 1.0 | 11 | 0.7 | 0.3 | 1.2 |
| | Candidiasis (10007152) | 7 | 0.4 | 0.2 | 0.9 | 6 | 0.4 | 0.1 | 0.8 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Cytomegalovirus infection (10011831) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Exanthema subitum (10015586) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis (10017888) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Nasopharyngitis (10028810) | 103 | 6.2 | 5.1 | 7.4 | 123 | 7.4 | 6.2 | 8.7 |
| | Otitis media (10033078) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Pharyngitis (10034835) | 6 | 0.4 | 0.1 | 0.8 | 8 | 0.5 | 0.2 | 0.9 |
| | Pneumonia (10035664) | 3 | 0.2 | 0.0 | 0.5 | 4 | 0.2 | 0.1 | 0.6 |
| | Pneumonia klebsiella (10035717) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tonsillitis (10044008) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.4 | 5 | 0.3 | 0.1 | 0.7 |
| | Tracheobronchitis (10044314) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 119 | 7.1 | 6.0 | 8.5 | 124 | 7.4 | 6.2 | 8.8 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Varicella (10046980) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.5 | 0.2 | 1.0 | 7 | 0.4 | 0.2 | 0.9 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 7 | 0.4 | 0.2 | 0.9 | 16 | 1.0 | 0.5 | 1.6 |
| | Nasal congestion (10028735) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |
| | Dermatitis allergic (10012434) | 6 | 0.4 | 0.1 | 0.8 | 3 | 0.2 | 0.0 | 0.5 |
| | Dermatitis diaper (10012444) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Eczema (10014184) | 1 | 0.1 | 0.0 | 0.3 | 4 | 0.2 | 0.1 | 0.6 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rash (10037844) | 3 | 0.2 | 0.0 | 0.5 | 5 | 0.3 | 0.1 | 0.7 |

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

**Table 222 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)**

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 356 | 10.9 | 9.9 | 12.0 | 420 | 12.9 | 11.7 | 14.1 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Heart disease congenital (10019273) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Hydrocele (10020488) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Thalassaemia (10043388) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Abdominal pain (10000081) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Constipation (10010774) | 16 | 0.5 | 0.3 | 0.8 | 10 | 0.3 | 0.1 | 0.6 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.2 | 6 | 0.2 | 0.1 | 0.4 |
| | Dyspepsia (10013946) | 8 | 0.2 | 0.1 | 0.5 | 7 | 0.2 | 0.1 | 0.4 |
| | Enteritis (10014866) | 6 | 0.2 | 0.1 | 0.4 | 14 | 0.4 | 0.2 | 0.7 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Mouth ulceration (10028034) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Vomiting (10047700) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Pyrexia (10037660) | 13 | 0.4 | 0.2 | 0.7 | 27 | 0.8 | 0.5 | 1.2 |

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hypersensitivity (10020751) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Bronchitis (10006451) | 18 | 0.6 | 0.3 | 0.9 | 27 | 0.8 | 0.5 | 1.2 |
| | Bronchopneumonia (10006469) | 9 | 0.3 | 0.1 | 0.5 | 11 | 0.3 | 0.2 | 0.6 |
| | Candidiasis (10007152) | 7 | 0.2 | 0.1 | 0.4 | 7 | 0.2 | 0.1 | 0.4 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Cytomegalovirus infection (10011831) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Exanthema subitum (10015586) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Gastroenteritis (10017888) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 110 | 3.4 | 2.8 | 4.0 | 131 | 4.0 | 3.4 | 4.7 |
| | Otitis media (10033078) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Pharyngitis (10034835) | 6 | 0.2 | 0.1 | 0.4 | 8 | 0.2 | 0.1 | 0.5 |
| | Pneumonia (10035664) | 3 | 0.1 | 0.0 | 0.3 | 4 | 0.1 | 0.0 | 0.3 |
| | Pneumonia klebsiella (10035717) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Tonsillitis (10044008) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.2 | 5 | 0.2 | 0.0 | 0.4 |
| | Tracheobronchitis (10044314) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Upper respiratory tract infection (10046306) | 126 | 3.9 | 3.2 | 4.6 | 134 | 4.1 | 3.5 | 4.8 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Varicella (10046980) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.3 | 0.1 | 0.5 | 8 | 0.2 | 0.1 | 0.5 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 8 | 0.2 | 0.1 | 0.5 | 16 | 0.5 | 0.3 | 0.8 |
| | Nasal congestion (10028735) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |
| | Dermatitis allergic (10012434) | 6 | 0.2 | 0.1 | 0.4 | 3 | 0.1 | 0.0 | 0.3 |
| | Dermatitis diaper (10012444) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Eczema (10014184) | 1 | 0.0 | 0.0 | 0.2 | 4 | 0.1 | 0.0 | 0.3 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rash (10037844) | 3 | 0.1 | 0.0 | 0.3 | 5 | 0.2 | 0.0 | 0.4 |

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

## Table 223 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |

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

## Table 224 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |

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

## Table 225 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 8 | 0.5 | 0.2 | 0.9 | 7 | 0.4 | 0.2 | 0.9 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.3 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Dyspepsia (10013946) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.1 | 0.0 | 0.3 | 4 | 0.2 | 0.1 | 0.6 |
| | Upper respiratory tract infection (10046306) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |

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

## Table 226 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort)

| | | HRV N = 3265 | | | | Placebo N = 3264 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 8 | 0.2 | 0.1 | 0.5 | 7 | 0.2 | 0.1 | 0.4 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Dyspepsia (10013946) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.0 | 0.0 | 0.2 | 4 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |

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

**Table 227 Percentage of subjects with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with reported during the entire study period (Total vaccinated cohort)**

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 445 | 26.7 | 24.6 | 28.9 | 525 | 31.5 | 29.3 | 33.8 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Lymphadenitis (10025188) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Cardiac disorders (10007541) | Myocarditis (10028606) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Cortical dysplasia (10070666) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 3 | 0.2 | 0.0 | 0.5 | 1 | 0.1 | 0.0 | 0.3 |
| | Heart disease congenital (10019273) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Hydrocele (10020488) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Patent ductus arteriosus (10034130) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Thalassaemia (10043388) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Thalassaemia beta (10043391) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Ventricular septal defect (10047298) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.5 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Abdominal pain (10000081) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Constipation (10010774) | 15 | 0.9 | 0.5 | 1.5 | 9 | 0.5 | 0.2 | 1.0 |
| | Diarrhoea (10012735) | 4 | 0.2 | 0.1 | 0.6 | 11 | 0.7 | 0.3 | 1.2 |
| | Dyspepsia (10013946) | 8 | 0.5 | 0.2 | 0.9 | 8 | 0.5 | 0.2 | 0.9 |
| | Enteritis (10014866) | 44 | 2.6 | 1.9 | 3.5 | 73 | 4.4 | 3.4 | 5.5 |
| | Food poisoning (10016952) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Gastrointestinal disorder (10017944) | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Inguinal hernia (10022016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Inguinal hernia, obstructive (10022021) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Intestinal obstruction (10022687) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Intussusception (10022863) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Mouth ulceration (10028034) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Vomiting (10047700) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| General disorders and administration site conditions (10018065) | Death (10011906) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Drowning (10013647) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Multi-organ failure (10028154) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Pyrexia (10037660) | 15 | 0.9 | 0.5 | 1.5 | 27 | 1.6 | 1.1 | 2.3 |
| Hepatobiliary disorders (10019805) | Hepatic function abnormal (10019670) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hypersensitivity (10020751) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 5 | 0.3 | 0.1 | 0.7 | 2 | 0.1 | 0.0 | 0.4 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchiolitis (10006448) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchitis (10006451) | 81 | 4.9 | 3.9 | 6.0 | 104 | 6.2 | 5.1 | 7.5 |
| | Bronchopneumonia (10006469) | 58 | 3.5 | 2.7 | 4.5 | 62 | 3.7 | 2.9 | 4.7 |
| | Candidiasis (10007152) | 8 | 0.5 | 0.2 | 0.9 | 7 | 0.4 | 0.2 | 0.9 |
| | Central nervous system infection (10061036) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Cytomegalovirus infection (10011831) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Diarrhoea infectious (10012742) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Exanthema subitum (10015586) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis (10017888) | 2 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.4 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Hand-foot-and-mouth disease (10019113) | 5 | 0.3 | 0.1 | 0.7 | 4 | 0.2 | 0.1 | 0.6 |
| | Herpangina (10019936) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Infectious mononucleosis (10021914) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Laryngitis (10023874) | 2 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.4 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Meningitis (10027199) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 111 | 6.7 | 5.5 | 8.0 | 127 | 7.6 | 6.4 | 9.0 |
| | Otitis media (10033078) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Pharyngitis (10034835) | 9 | 0.5 | 0.2 | 1.0 | 16 | 1.0 | 0.5 | 1.6 |
| | Pneumonia (10035664) | 15 | 0.9 | 0.5 | 1.5 | 14 | 0.8 | 0.5 | 1.4 |
| | Pneumonia klebsiella (10035717) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Shigella infection (10054178) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Tonsillitis (10044008) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Tracheitis (10044302) | 7 | 0.4 | 0.2 | 0.9 | 9 | 0.5 | 0.2 | 1.0 |
| | Tracheobronchitis (10044314) | 5 | 0.3 | 0.1 | 0.7 | 1 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 136 | 8.2 | 6.9 | 9.6 | 151 | 9.1 | 7.7 | 10.5 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Varicella (10046980) | 2 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.3 |
| Injury, poisoning and procedural complications (10022117) | Brain contusion (10052346) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Brain herniation (10006126) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Skull fracture (10061365) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.5 | 0.2 | 1.0 | 8 | 0.5 | 0.2 | 0.9 |
| | Liver function test abnormal (10024690) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Dehydration (10012174) | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| | Hypokalaemia (10021015) | 1 | 0.1 | 0.0 | 0.3 | 3 | 0.2 | 0.0 | 0.5 |
| | Hyponatraemia (10021036) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104) | Acute lymphocytic leukaemia (10000846) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Histiocytosis haematophagic (10048595) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Cerebral haematoma (10053942) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Convulsion (10010904) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Epilepsy (10015037) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Febrile convulsion (10016284) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.4 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Subarachnoid haemorrhage (10042316) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Renal and urinary disorders (10038359) | Hydronephrosis (10020524) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Ureteric stenosis (10046411) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Asphyxia (10003497) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Asthma (10003553) | 3 | 0.2 | 0.0 | 0.5 | 1 | 0.1 | 0.0 | 0.3 |

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Cough (10011224) | 7 | 0.4 | 0.2 | 0.9 | 18 | 1.1 | 0.6 | 1.7 |
| | Nasal congestion (10028735) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Respiratory failure (10038695) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rhinorrhoea (10039101) | 3 | 0.2 | 0.0 | 0.5 | 4 | 0.2 | 0.1 | 0.6 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 4 | 0.2 | 0.1 | 0.6 | 1 | 0.1 | 0.0 | 0.3 |
| | Dermatitis allergic (10012434) | 8 | 0.5 | 0.2 | 0.9 | 3 | 0.2 | 0.0 | 0.5 |
| | Dermatitis diaper (10012444) | 1 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.3 |
| | Eczema (10014184) | 1 | 0.1 | 0.0 | 0.3 | 4 | 0.2 | 0.1 | 0.6 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Rash (10037844) | 3 | 0.2 | 0.0 | 0.5 | 5 | 0.3 | 0.1 | 0.7 |
| | Urticaria (10046735) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |

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

**Table 228 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| **At least one symptom** | | 258 | 17.1 | 15.2 | 19.0 | 312 | 20.6 | 18.6 | 22.7 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.5 |
| | Heart disease congenital (10019273) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.5 | 3 | 0.2 | 0.0 | 0.6 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.5 | 0 | 0.0 | 0.0 | 0.2 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Abdominal pain (10000081) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Constipation (10010774) | 15 | 1.0 | 0.6 | 1.6 | 9 | 0.6 | 0.3 | 1.1 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.5 | 6 | 0.4 | 0.1 | 0.9 |
| | Dyspepsia (10013946) | 7 | 0.5 | 0.2 | 1.0 | 6 | 0.4 | 0.1 | 0.9 |
| | Enteritis (10014866) | 5 | 0.3 | 0.1 | 0.8 | 11 | 0.7 | 0.4 | 1.3 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.5 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Mouth ulceration (10028034) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Vomiting (10047700) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Pyrexia (10037660) | 10 | 0.7 | 0.3 | 1.2 | 24 | 1.6 | 1.0 | 2.3 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Hypersensitivity (10020751) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.5 | 0 | 0.0 | 0.0 | 0.2 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Bronchitis (10006451) | 16 | 1.1 | 0.6 | 1.7 | 22 | 1.5 | 0.9 | 2.2 |
| | Bronchopneumonia (10006469) | 7 | 0.5 | 0.2 | 1.0 | 9 | 0.6 | 0.3 | 1.1 |
| | Candidiasis (10007152) | 6 | 0.4 | 0.1 | 0.9 | 6 | 0.4 | 0.1 | 0.9 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Cytomegalovirus infection (10011831) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Exanthema subitum (10015586) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis (10017888) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Nasopharyngitis (10028810) | 83 | 5.5 | 4.4 | 6.8 | 108 | 7.1 | 5.9 | 8.5 |
| | Pharyngitis (10034835) | 5 | 0.3 | 0.1 | 0.8 | 8 | 0.5 | 0.2 | 1.0 |
| | Pneumonia (10035664) | 1 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.5 |
| | Pneumonia klebsiella (10035717) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Tonsillitis (10044008) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.5 | 3 | 0.2 | 0.0 | 0.6 |
| | Tracheobronchitis (10044314) | 4 | 0.3 | 0.1 | 0.7 | 1 | 0.1 | 0.0 | 0.4 |
| | Upper respiratory tract infection (10046306) | 89 | 5.9 | 4.8 | 7.2 | 98 | 6.5 | 5.3 | 7.8 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.5 | 0 | 0.0 | 0.0 | 0.2 |
| | Varicella (10046980) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.6 | 0.3 | 1.1 | 7 | 0.5 | 0.2 | 1.0 |
| Metabolism and nutrition disorders (10027433) | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.5 |

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 6 | 0.4 | 0.1 | 0.9 | 13 | 0.9 | 0.5 | 1.5 |
| | Nasal congestion (10028735) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.5 | 3 | 0.2 | 0.0 | 0.6 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 3 | 0.2 | 0.0 | 0.6 | 1 | 0.1 | 0.0 | 0.4 |
| | Dermatitis allergic (10012434) | 6 | 0.4 | 0.1 | 0.9 | 3 | 0.2 | 0.0 | 0.6 |
| | Eczema (10014184) | 1 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.6 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Rash (10037844) | 3 | 0.2 | 0.0 | 0.6 | 5 | 0.3 | 0.1 | 0.8 |

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

**Table 229 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort-except immunogenicity sub-cohort 2)**

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 292 | 9.9 | 8.8 | 11.0 | 354 | 12.0 | 10.8 | 13.2 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Heart disease congenital (10019273) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Eye disorders (10015919) | Conjunctivitis (10010741) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Dacryostenosis acquired (10053990) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Gastrointestinal disorders (10017947) | Abdominal discomfort (10000059) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Abdominal distension (10000060) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Abdominal pain (10000081) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Aphthous stomatitis (10002958) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Constipation (10010774) | 16 | 0.5 | 0.3 | 0.9 | 10 | 0.3 | 0.2 | 0.6 |
| | Diarrhoea (10012735) | 2 | 0.1 | 0.0 | 0.2 | 6 | 0.2 | 0.1 | 0.4 |
| | Dyspepsia (10013946) | 7 | 0.2 | 0.1 | 0.5 | 6 | 0.2 | 0.1 | 0.4 |
| | Enteritis (10014866) | 5 | 0.2 | 0.1 | 0.4 | 11 | 0.4 | 0.2 | 0.7 |
| | Gastritis (10017853) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Gastrooesophageal reflux disease (10017885) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Mouth ulceration (10028034) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Tongue ulceration (10043991) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Vomiting (10047700) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| General disorders and administration site conditions (10018065) | Hernia (10019909) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Irritability (10022998) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Pyrexia (10037660) | 10 | 0.3 | 0.2 | 0.6 | 24 | 0.8 | 0.5 | 1.2 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hypersensitivity (10020751) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Acute tonsillitis (10001093) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Bacterial diarrhoea (10004016) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Bronchitis (10006451) | 16 | 0.5 | 0.3 | 0.9 | 22 | 0.7 | 0.5 | 1.1 |

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| | Bronchopneumonia (10006469) | 7 | 0.2 | 0.1 | 0.5 | 9 | 0.3 | 0.1 | 0.6 |
| | Candidiasis (10007152) | 6 | 0.2 | 0.1 | 0.4 | 7 | 0.2 | 0.1 | 0.5 |
| | Cystitis (10011781) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Cytomegalovirus infection (10011831) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Exanthema subitum (10015586) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Gastroenteritis (10017888) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hand-foot-and-mouth disease (10019113) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Herpangina (10019936) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Lobar pneumonia (10024738) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 89 | 3.0 | 2.4 | 3.7 | 115 | 3.9 | 3.2 | 4.6 |
| | Pharyngitis (10034835) | 5 | 0.2 | 0.1 | 0.4 | 8 | 0.3 | 0.1 | 0.5 |
| | Pneumonia (10035664) | 1 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.2 |
| | Pneumonia klebsiella (10035717) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Pneumonia staphylococcal (10035734) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Respiratory tract infection (10062352) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinitis (10039083) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Tonsillitis (10044008) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Tracheitis (10044302) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Tracheobronchitis (10044314) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |
| | Upper respiratory tract infection (10046306) | 94 | 3.2 | 2.6 | 3.9 | 106 | 3.6 | 2.9 | 4.3 |
| | Urethritis (10046480) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Varicella (10046980) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| Investigations (10022891) | Cold agglutinins positive (10009854) | 9 | 0.3 | 0.1 | 0.6 | 8 | 0.3 | 0.1 | 0.5 |
| Metabolism and nutrition disorders (10027433) | Decreased appetite (10061428) | 0 | 0.0 | 0.0 | 0.1 | 2 | 0.1 | 0.0 | 0.2 |
| | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| Nervous system disorders (10029205) | Convulsion (10010904) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| | Hydrocephalus (10020508) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Pregnancy, puerperium and perinatal conditions (10036585) | Jaundice neonatal (10023138) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 7 | 0.2 | 0.1 | 0.5 | 13 | 0.4 | 0.2 | 0.7 |
| | Nasal congestion (10028735) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Nasal obstruction (10028748) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rhinorrhoea (10039101) | 2 | 0.1 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 3 | 0.1 | 0.0 | 0.3 | 1 | 0.0 | 0.0 | 0.2 |
| | Dermatitis allergic (10012434) | 6 | 0.2 | 0.1 | 0.4 | 3 | 0.1 | 0.0 | 0.3 |
| | Eczema (10014184) | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Eczema infantile (10014198) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Hyperhidrosis (10020642) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Rash (10037844) | 3 | 0.1 | 0.0 | 0.3 | 5 | 0.2 | 0.1 | 0.4 |

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

**Table 230 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 1 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.5 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |

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

**Table 231 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 1 | 0.0 | 0.0 | 0.2 | 2 | 0.1 | 0.0 | 0.2 |
| Metabolism and nutrition disorders (10027433) | Malnutrition (10061273) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| Nervous system disorders (10029205) | Extrapyramidal disorder (10015832) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Haemorrhage intracranial (10018985) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |

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

**Table 232 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 1513 | | | | Placebo N = 1514 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 5 | 0.3 | 0.1 | 0.8 | 6 | 0.4 | 0.1 | 0.9 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.5 | 1 | 0.1 | 0.0 | 0.4 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.4 |
| | Dyspepsia (10013946) | 1 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.1 | 0.0 | 0.4 | 3 | 0.2 | 0.0 | 0.6 |
| | Upper respiratory tract infection (10046306) | 1 | 0.1 | 0.0 | 0.4 | 1 | 0.1 | 0.0 | 0.4 |

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

**Table 233 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)**

| | | HRV N = 2962 | | | | Placebo N = 2960 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 5 | 0.2 | 0.1 | 0.4 | 6 | 0.2 | 0.1 | 0.4 |
| Gastrointestinal disorders (10017947) | Constipation (10010774) | 2 | 0.1 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.0 | 0.0 | 0.2 |
| | Dyspepsia (10013946) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.1 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.1 | 0.0 | 0.3 |
| | Upper respiratory tract infection (10046306) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.0 | 0.0 | 0.2 |

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

**Table 234 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV N = 153 | | | | Placebo N = 153 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | 52 | 34.0 | 26.5 | 42.1 | 56 | 36.6 | 29.0 | 44.8 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.7 | 0.0 | 3.6 | 1 | 0.7 | 0.0 | 3.6 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| Congenital, familial and genetic disorders (10010331) | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 1.3 | 0.2 | 4.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Hydrocele (10020488) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Thalassaemia (10043388) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| Gastrointestinal disorders (10017947) | Dyspepsia (10013946) | 1 | 0.7 | 0.0 | 3.6 | 1 | 0.7 | 0.0 | 3.6 |
| | Enteritis (10014866) | 1 | 0.7 | 0.0 | 3.6 | 3 | 2.0 | 0.4 | 5.6 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| General disorders and administration site conditions (10018065) | Pyrexia (10037660) | 3 | 2.0 | 0.4 | 5.6 | 3 | 2.0 | 0.4 | 5.6 |
| Infections and infestations (10021881) | Bronchitis (10006451) | 2 | 1.3 | 0.2 | 4.6 | 5 | 3.3 | 1.1 | 7.5 |
| | Bronchopneumonia (10006469) | 2 | 1.3 | 0.2 | 4.6 | 2 | 1.3 | 0.2 | 4.6 |
| | Candidiasis (10007152) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Nasopharyngitis (10028810) | 20 | 13.1 | 8.2 | 19.5 | 15 | 9.8 | 5.6 | 15.7 |
| | Otitis media (10033078) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Pharyngitis (10034835) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Pneumonia (10035664) | 2 | 1.3 | 0.2 | 4.6 | 2 | 1.3 | 0.2 | 4.6 |
| | Tracheitis (10044302) | 0 | 0.0 | 0.0 | 2.4 | 2 | 1.3 | 0.2 | 4.6 |
| | Upper respiratory tract infection (10046306) | 30 | 19.6 | 13.6 | 26.8 | 26 | 17.0 | 11.4 | 23.9 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 1 | 0.7 | 0.0 | 3.6 | 3 | 2.0 | 0.4 | 5.6 |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Dermatitis diaper (10012444) | 1 | 0.7 | 0.0 | 3.6 | 0 | 0.0 | 0.0 | 2.4 |
| | Eczema (10014184) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |

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

**Table 235 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort-Immunogenicity sub-cohort 2)**

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 64 | 21.1 | 16.7 | 26.2 | 66 | 21.7 | 17.2 | 26.8 |
| Blood and lymphatic system disorders (10005329) | Anaemia (10002034) | 1 | 0.3 | 0.0 | 1.8 | 1 | 0.3 | 0.0 | 1.8 |
| | Deficiency anaemia (10061101) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| Congenital, familial and genetic disorders (10010331) | Glucose-6-phosphate dehydrogenase deficiency (10018444) | 2 | 0.7 | 0.1 | 2.4 | 0 | 0.0 | 0.0 | 1.2 |
| | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Hydrocele (10020488) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Thalassaemia (10043388) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| Gastrointestinal disorders (10017947) | Dyspepsia (10013946) | 1 | 0.3 | 0.0 | 1.8 | 1 | 0.3 | 0.0 | 1.8 |
| | Enteritis (10014866) | 1 | 0.3 | 0.0 | 1.8 | 3 | 1.0 | 0.2 | 2.9 |
| | Stomatitis (10042128) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| General disorders and administration site conditions (10018065) | Pyrexia (10037660) | 3 | 1.0 | 0.2 | 2.9 | 3 | 1.0 | 0.2 | 2.9 |
| Infections and infestations (10021881) | Bronchitis (10006451) | 2 | 0.7 | 0.1 | 2.4 | 5 | 1.6 | 0.5 | 3.8 |
| | Bronchopneumonia (10006469) | 2 | 0.7 | 0.1 | 2.4 | 2 | 0.7 | 0.1 | 2.4 |
| | Candidiasis (10007152) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Gastroenteritis bacterial (10061166) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Herpes virus infection (10019973) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Nasopharyngitis (10028810) | 21 | 6.9 | 4.3 | 10.4 | 16 | 5.3 | 3.0 | 8.4 |
| | Otitis media (10033078) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Pharyngitis (10034835) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Pneumonia (10035664) | 2 | 0.7 | 0.1 | 2.4 | 2 | 0.7 | 0.1 | 2.4 |
| | Tracheitis (10044302) | 0 | 0.0 | 0.0 | 1.2 | 2 | 0.7 | 0.1 | 2.4 |
| | Upper respiratory tract infection (10046306) | 32 | 10.6 | 7.3 | 14.6 | 28 | 9.2 | 6.2 | 13.0 |
| Metabolism and nutrition disorders (10027433) | Acidosis (10000486) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Cough (10011224) | 1 | 0.3 | 0.0 | 1.8 | 3 | 1.0 | 0.2 | 2.9 |

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| Skin and subcutaneous tissue disorders (10040785) | Dermatitis (10012431) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Dermatitis diaper (10012444) | 1 | 0.3 | 0.0 | 1.8 | 0 | 0.0 | 0.0 | 1.2 |
| | Eczema (10014184) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |

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

## Table 236 Percentage of subjects reporting the occurrence of grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | HRV N = 153 | | | | Placebo N = 153 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |

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

## Table 237 Percentage of doses with grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| Congenital, familial and genetic disorders (10010331) | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |

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

**Table 238 Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV N = 153 | | | | Placebo N = 153 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 3 | 2.0 | 0.4 | 5.6 | 1 | 0.7 | 0.0 | 3.6 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 0 | 0.0 | 0.0 | 2.4 | 1 | 0.7 | 0.0 | 3.6 |
| | Upper respiratory tract infection (10046306) | 3 | 2.0 | 0.4 | 5.6 | 0 | 0.0 | 0.0 | 2.4 |

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

**Table 239 Percentage of doses with unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term with causal relationship to vaccination, within the 31-day (Days 0-30) post-vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)**

| | | HRV N = 303 | | | | Placebo N = 304 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| Primary System Organ Class (CODE) | Preferred Term (CODE) | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | | 3 | 1.0 | 0.2 | 2.9 | 1 | 0.3 | 0.0 | 1.8 |
| Infections and infestations (10021881) | Nasopharyngitis (10028810) | 0 | 0.0 | 0.0 | 1.2 | 1 | 0.3 | 0.0 | 1.8 |
| | Upper respiratory tract infection (10046306) | 3 | 1.0 | 0.2 | 2.9 | 0 | 0.0 | 0.0 | 1.2 |

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

## 11.6.2. Serious adverse events

### 11.6.2.1. Fatal events

**Table 240 Listings of fatalities from dose 1 of HRV or Placebo up to visit 7 (Total vaccinated cohort)**

| Group | Dose | Day since last dose | Pid | Case ID | Sex | Day since dose 1 | Date of death | Age at death (days) | Verbatim |
|---|---|---|---|---|---|---|---|---|---|
| This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register. | | | | | | | | | |

### 11.6.2.2. Non-fatal events

Refer section 14.1.

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

### Table 241 Percentage of subjects reporting the occurrence of AEs/SAEs leading to drop out from the study classified by MedDRA Primary System Organ Class and Preferred Term during the study period (Total vaccinated cohort)

| | | HRV N = 1666 | | | | Placebo N = 1667 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | |
| **Primary System Organ Class (CODE)** | **Preferred Term (CODE)** | **n** | **%** | **LL** | **UL** | **n** | **%** | **LL** | **UL** |
| At least one symptom | | 8 | 0.5 | 0.2 | 0.9 | 10 | 0.6 | 0.3 | 1.1 |
| Congenital, familial and genetic disorders (10010331) | Atrial septal defect (10003664) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Cortical dysplasia (10070666) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Heart disease congenital (10019273) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Gastrointestinal disorders (10017947) | Diarrhoea (10012735) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| General disorders and administration site conditions (10018065) | Drowning (10013647) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Multi-organ failure (10028154) | 1 | 0.1 | 0.0 | 0.3 | 2 | 0.1 | 0.0 | 0.4 |
| Infections and infestations (10021881) | Bronchitis (10006451) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Bronchopneumonia (10006469) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Central nervous system infection (10061036) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Diarrhoea infectious (10012742) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Meningitis (10027199) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Nasopharyngitis (10028810) | 2 | 0.1 | 0.0 | 0.4 | 2 | 0.1 | 0.0 | 0.4 |
| Injury, poisoning and procedural complications (10022117) | Brain contusion (10052346) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Brain herniation (10006126) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Skull fracture (10061365) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104) | Acute lymphocytic leukaemia (10000846) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Nervous system disorders (10029205) | Cerebral haematoma (10053942) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| | Haemorrhage intracranial (10018985) | 1 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.2 |
| | Subarachnoid haemorrhage (10042316) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Asphyxia (10003497) | 2 | 0.1 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.2 |
| | Respiratory failure (10038695) | 0 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.3 |

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

## 11.6.4. Concomitant medications /vaccinations

### Table 242 Incidence of concomitant medication within the 8-day (Days 0-7) post vaccination period (Total vaccinated cohort- except immunogenicity sub-cohort 2)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 1513 | 73 | 4.8 | 3.8 | 6.0 | 1514 | 109 | 7.2 | 5.9 | 8.6 |
| Any antipyretic | 1513 | 9 | 0.6 | 0.3 | 1.1 | 1514 | 20 | 1.3 | 0.8 | 2.0 |
| Prophylactic antipyretic | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1513 | 18 | 1.2 | 0.7 | 1.9 | 1514 | 24 | 1.6 | 1.0 | 2.3 |
| **Dose 2** | | | | | | | | | | |
| Any | 1449 | 84 | 5.8 | 4.7 | 7.1 | 1446 | 80 | 5.5 | 4.4 | 6.8 |
| Any antipyretic | 1449 | 12 | 0.8 | 0.4 | 1.4 | 1446 | 14 | 1.0 | 0.5 | 1.6 |
| Prophylactic antipyretic | 1449 | 0 | 0.0 | 0.0 | 0.3 | 1446 | 0 | 0.0 | 0.0 | 0.3 |
| Any antibiotic | 1449 | 23 | 1.6 | 1.0 | 2.4 | 1446 | 33 | 2.3 | 1.6 | 3.2 |
| **Overall/dose** | | | | | | | | | | |
| Any | 2962 | 157 | 5.3 | 4.5 | 6.2 | 2960 | 189 | 6.4 | 5.5 | 7.3 |
| Any antipyretic | 2962 | 21 | 0.7 | 0.4 | 1.1 | 2960 | 34 | 1.1 | 0.8 | 1.6 |
| Prophylactic antipyretic | 2962 | 0 | 0.0 | 0.0 | 0.1 | 2960 | 0 | 0.0 | 0.0 | 0.1 |
| Any antibiotic | 2962 | 41 | 1.4 | 1.0 | 1.9 | 2960 | 57 | 1.9 | 1.5 | 2.5 |
| **Overall/subject** | | | | | | | | | | |
| Any | 1513 | 137 | 9.1 | 7.7 | 10.6 | 1514 | 174 | 11.5 | 9.9 | 13.2 |
| Any antipyretic | 1513 | 20 | 1.3 | 0.8 | 2.0 | 1514 | 32 | 2.1 | 1.5 | 3.0 |
| Prophylactic antipyretic | 1513 | 0 | 0.0 | 0.0 | 0.2 | 1514 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1513 | 36 | 2.4 | 1.7 | 3.3 | 1514 | 57 | 3.8 | 2.9 | 4.9 |

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

## Table 243 Incidence of concomitant medication within the 8-day (Days 0-7) post vaccination period (Total vaccinated cohort- Immunogenicity sub-cohort 2)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 153 | 10 | 6.5 | 3.2 | 11.7 | 153 | 9 | 5.9 | 2.7 | 10.9 |
| Any antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| Prophylactic antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| Any antibiotic | 153 | 6 | 3.9 | 1.5 | 8.3 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| **Dose 2** | | | | | | | | | | |
| Any | 150 | 11 | 7.3 | 3.7 | 12.7 | 151 | 8 | 5.3 | 2.3 | 10.2 |
| Any antipyretic | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 2 | 1.3 | 0.2 | 4.7 |
| Prophylactic antipyretic | 150 | 0 | 0.0 | 0.0 | 2.4 | 151 | 0 | 0.0 | 0.0 | 2.4 |
| Any antibiotic | 150 | 3 | 2.0 | 0.4 | 5.7 | 151 | 4 | 2.6 | 0.7 | 6.6 |
| **Overall/dose** | | | | | | | | | | |
| Any | 303 | 21 | 6.9 | 4.3 | 10.4 | 304 | 17 | 5.6 | 3.3 | 8.8 |
| Any antipyretic | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 2 | 0.7 | 0.1 | 2.4 |
| Prophylactic antipyretic | 303 | 0 | 0.0 | 0.0 | 1.2 | 304 | 0 | 0.0 | 0.0 | 1.2 |
| Any antibiotic | 303 | 9 | 3.0 | 1.4 | 5.6 | 304 | 6 | 2.0 | 0.7 | 4.2 |
| **Overall/subject** | | | | | | | | | | |
| Any | 153 | 21 | 13.7 | 8.7 | 20.2 | 153 | 17 | 11.1 | 6.6 | 17.2 |
| Any antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 2 | 1.3 | 0.2 | 4.6 |
| Prophylactic antipyretic | 153 | 0 | 0.0 | 0.0 | 2.4 | 153 | 0 | 0.0 | 0.0 | 2.4 |
| Any antibiotic | 153 | 9 | 5.9 | 2.7 | 10.9 | 153 | 6 | 3.9 | 1.5 | 8.3 |

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

## Table 244 Incidence of concomitant medication within the 8-day (Days 0-7) post vaccination period (Total vaccinated cohort)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 1666 | 83 | 5.0 | 4.0 | 6.1 | 1667 | 118 | 7.1 | 5.9 | 8.4 |
| Any antipyretic | 1666 | 9 | 0.5 | 0.2 | 1.0 | 1667 | 20 | 1.2 | 0.7 | 1.8 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 24 | 1.4 | 0.9 | 2.1 | 1667 | 26 | 1.6 | 1.0 | 2.3 |
| **Dose 2** | | | | | | | | | | |
| Any | 1599 | 95 | 5.9 | 4.8 | 7.2 | 1597 | 88 | 5.5 | 4.4 | 6.7 |
| Any antipyretic | 1599 | 12 | 0.8 | 0.4 | 1.3 | 1597 | 16 | 1.0 | 0.6 | 1.6 |
| Prophylactic antipyretic | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1599 | 26 | 1.6 | 1.1 | 2.4 | 1597 | 37 | 2.3 | 1.6 | 3.2 |
| **Overall/dose** | | | | | | | | | | |
| Any | 3265 | 178 | 5.5 | 4.7 | 6.3 | 3264 | 206 | 6.3 | 5.5 | 7.2 |
| Any antipyretic | 3265 | 21 | 0.6 | 0.4 | 1.0 | 3264 | 36 | 1.1 | 0.8 | 1.5 |
| Prophylactic antipyretic | 3265 | 0 | 0.0 | 0.0 | 0.1 | 3264 | 0 | 0.0 | 0.0 | 0.1 |
| Any antibiotic | 3265 | 50 | 1.5 | 1.1 | 2.0 | 3264 | 63 | 1.9 | 1.5 | 2.5 |
| **Overall/subject** | | | | | | | | | | |
| Any | 1666 | 158 | 9.5 | 8.1 | 11.0 | 1667 | 191 | 11.5 | 10.0 | 13.1 |
| Any antipyretic | 1666 | 20 | 1.2 | 0.7 | 1.8 | 1667 | 34 | 2.0 | 1.4 | 2.8 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 45 | 2.7 | 2.0 | 3.6 | 1667 | 63 | 3.8 | 2.9 | 4.8 |

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

## Table 245 Incidence of concomitant medication during the entire study period (Total vaccinated cohort)

| | HRV | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | | 95% CI | |
| | N | n | % | LL | UL | N | n | % | LL | UL |
| **Dose 1** | | | | | | | | | | |
| Any | 1666 | 222 | 13.3 | 11.7 | 15.1 | 1667 | 287 | 17.2 | 15.4 | 19.1 |
| Any antipyretic | 1666 | 30 | 1.8 | 1.2 | 2.6 | 1667 | 48 | 2.9 | 2.1 | 3.8 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 78 | 4.7 | 3.7 | 5.8 | 1667 | 95 | 5.7 | 4.6 | 6.9 |
| **Dose 2** | | | | | | | | | | |
| Any | 1599 | 457 | 28.6 | 26.4 | 30.9 | 1597 | 485 | 30.4 | 28.1 | 32.7 |
| Any antipyretic | 1599 | 96 | 6.0 | 4.9 | 7.3 | 1597 | 105 | 6.6 | 5.4 | 7.9 |
| Prophylactic antipyretic | 1599 | 0 | 0.0 | 0.0 | 0.2 | 1597 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1599 | 263 | 16.4 | 14.7 | 18.4 | 1597 | 311 | 19.5 | 17.6 | 21.5 |
| **Overall/dose** | | | | | | | | | | |
| Any | 3562 | 679 | 19.1 | 17.8 | 20.4 | 3562 | 772 | 21.7 | 20.3 | 23.1 |
| Any antipyretic | 3562 | 126 | 3.5 | 3.0 | 4.2 | 3562 | 153 | 4.3 | 3.7 | 5.0 |
| Prophylactic antipyretic | 3562 | 0 | 0.0 | 0.0 | 0.1 | 3562 | 0 | 0.0 | 0.0 | 0.1 |
| Any antibiotic | 3562 | 341 | 9.6 | 8.6 | 10.6 | 3562 | 406 | 11.4 | 10.4 | 12.5 |
| **Overall/subject** | | | | | | | | | | |
| Any | 1666 | 576 | 34.6 | 32.3 | 36.9 | 1667 | 644 | 38.6 | 36.3 | 41.0 |
| Any antipyretic | 1666 | 121 | 7.3 | 6.1 | 8.6 | 1667 | 144 | 8.6 | 7.3 | 10.1 |
| Prophylactic antipyretic | 1666 | 0 | 0.0 | 0.0 | 0.2 | 1667 | 0 | 0.0 | 0.0 | 0.2 |
| Any antibiotic | 1666 | 310 | 18.6 | 16.8 | 20.6 | 1667 | 375 | 22.5 | 20.5 | 24.6 |

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

# 12. REFERENCES (CONTENTS OF MAJOR REFERENCES)

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***Linhares AC, Valazquez FR, Perez-Schael I, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the fi rst 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet. 2008; 371: 1181–89***

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Zou G.Y, Donner A. Construction of confidence limits about effect measures: a general approach, *Statist. Med*. 2008; 27:1693–1702).

**(Amended 14 August 2013)**

# 13. STUDY REPORT AUTHORS /CONTRIBUTING AUTHORS

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Lead Statistician Rotavirus Vaccine
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Central Safety Physician: [redacted]

Clinical Development Manager (CDM): [redacted]

Regulatory Affairs representative: [redacted] ***and*** [redacted]

Lead CDM: [redacted]

**(Amended 14 August 2013)**

## 14.2. CIOMS reports

*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 |
| Randomisation list (patient identification and treatment assigned) | 16.1.7 |
| Audit certificates (if available) | 16.1.8 |
| Documentation of statistical methods | 16.1.9 |
| Documentation of inter-laboratory standardisation 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)<br>CRFs /eCRFs for deaths, other SAEs and withdrawals due to adverse events | 16.3<br>16.3.1 |

# Sponsor Information

# Sponsor Information Sheet

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of document** | 13 June 2011 |
| **Version of document** | 13.1 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |

## 1. Country

China

## 2. Co-ordinating Investigator

[redacted]

[redacted] China
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Fax: [redacted]
E-mail: [redacted]

## 3. Medical Monitor

[redacted]

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E-mail: [redacted]

## 4. Study Monitor

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GlaxoSmithKline (China) Investment Co., Ltd.
9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
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**Back up:**

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GlaxoSmithKline (China) Investment Co., Ltd.
9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

**5. Study Contact for Reporting of a Serious Adverse Event**

Study Contact for Reporting SAEs (China)

[redacted]

GlaxoSmithKline (China) Investment Co., Ltd.
9/F Tower A, Ocean International Centre, No.56 Mid 4th East Ring Rd, Beijing 100025, China
Tel: [redacted]
Fax: [redacted]
E-mail: [redacted]

Back-up Study Contact for Reporting SAEs (Belgium)

GSK Biologicals Clinical Safety Physician
Fax: [redacted] or [redacted]
24/24 hour and 7/7 day availability

**6. Study Contact for Emergency Code Break**

Mobile phones for 7/7 day availability:
Outside US/Canada:
[redacted] (GSK Biologicals Central Safety Physician)
Back-up mobile phone contact (all countries): [redacted]

**7. Study Centres**

[redacted] China

[redacted] China

[redacted] China

[redacted] China.

# Protocol and Protocol Amendments

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**Clinical Study Protocol**
Sponsor:
**GlaxoSmithKline Biologicals**
Rue de l'Institut 89,1330 Rixensart, Belgium

| | |
|---|---|
| **Primary Study vaccine** | Liquid formulation of GlaxoSmithKline (GSK) Biologicals' oral live attenuated human rotavirus (HRV) vaccine (444563) |
| **Other Study vaccines** | • GSK Biologicals' Placebo for liquid HRV vaccine.<br>• GSK Biologicals' Diphtheria-tetanus- acellular pertussis vaccine (DTPa).<br>• Institute of Medical Biology Chinese Academy of Medical Sciences' Oral poliovirus vaccine (OPV). |
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **Investigational New Drug (IND) number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Title** | Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Co-ordinating author** | [redacted] Scientific Writer |
| **Contributing authors** | • [redacted] Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA<br>• [redacted] MD., PhD., Senior Manager, GCDC, USA<br>• [redacted] Project Statistician, CDOC-B |

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113808 (ROTA-075)
Amendment 2

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **Investigational New Drug (IND) number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Title** | Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Contributing authors** | • [redacted] Global Study Manager, GCRD<br>• [redacted] Manager Biometrics, CDOC-B<br>• [redacted] Safety Scientist, SERM<br>• [redacted] Manager, R&D Laboratory<br>• [redacted] ***Clinical Immunology representative***<br>• [redacted] Clinical Data Coordinator, CDOC-B<br>• [redacted] Medical Director, GSK Biologicals – China and Hong Kong<br>• [redacted] Head of Clinical R&D, China<br>• [redacted] Senior Medical Affairs Manager, China |

***GSK Biologicals' Protocol DS v 13.1***

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113808 (ROTA-075)
Amendment 2

# Protocol Amendment 2 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010. |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted]<br>Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | _____ |
| **Date** | _____ |

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113808 (ROTA-075)
Amendment 2

# Protocol Amendment 2 Rationale

| **Amendment number:** Amendment 2 |
|---|
| **Rationale/background for changes:** Based on the preliminary review of GE episodes reported to date prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seems lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up needs to be extended till April 2012 (i.e. end of RV season in China).<br>• Section 1.1: Background<br>• Synopsis and Section 1.2: Rationale for the study and study design<br>• Synopsis and Section 3: Study Design Overview<br>• Section 4.1: Number of subjects/centres<br>• Section 5.5: Outline of study procedures<br>• Section 5.6.3.12: Recording GE occurring throughout the study period in a GE diary card<br>• Section 5.6.3.13: Collection of stool samples in case the child develops GE<br>• Section 5.6.3.14: Return of diary cards and GE diary cards<br>• Section 5.6.3.15: Diary card and GE diary card transcription by investigator<br>• Section 5.6.4 Procedures during Efficacy follow-up (Visit 6)<br>• Section 5.6.5 Procedures during Efficacy follow-up (Visit 7)<br>• Section 5.7.2: Biological samples<br>• Section 5.7.3: Laboratory Assays<br>• Section 6.7.2: Time window for recording concomitant medication/vaccination in the eCRF<br>• Section 8.3.1: Time period for detecting and recording adverse events, serious adverse events<br>• Synopsis and Section 10.1: Primary endpoint<br>• Synopsis and Section 10.2: Secondary endpoints<br>• Section 10.3: Estimated sample size<br>• Section 10.5: Derived and transformed data<br>• Section 10.6.1: Sequence of analyses<br>• Section 10.7.2: Analysis of efficacy<br>• Section 10.7.4: Analysis of safety |

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113808 (ROTA-075)
Amendment 2

# Protocol Amendment 2 Investigator Agreement

**I agree:**

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (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.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- 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 updated Curriculum Vitae and other documents required by regulatory agencies for this study.

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113808 (ROTA-075)
Amendment 2

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | |
| **Signature** | |
| **Date** | |

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# SYNOPSIS

**Detailed Title**

A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.

**Indication**

Active immunisation of infants against gastroenteritis (GE) due to rotavirus (RV).

**Rationale for the study and study design**

– **Rationale for the study and study design**

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of file for licensure in China.

The primary objective of this study is to evaluate the efficacy of the liquid HRV vaccine to prevent severe RV GE during the efficacy follow-up period. There will be an efficacy follow-up starting 2 weeks after the second dose of study vaccination till ***April 2012 (i.e. end of RV season in China)***. **Amended: 05 August 2011.**

GSK Biologicals also intends to submit immunogenicity and reactogenicity data of the liquid HRV vaccine and co-administered routine vaccines to the regulatory authorities. In order to assess the immunogenicity of the study vaccines, two immunogenicity sub-cohorts are planned to be enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo will be assessed in the first sub-cohort (N = 600). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 will be assessed in the second sub-cohort (N = 300). Reactogenicity of the liquid HRV vaccine/Placebo will be assessed in the whole cohort except immunogenicity second sub-cohort.

– **Rationale for the use of placebo**

As per recommendations of the regulatory authorities in China, it is suggested to include a control group in vaccine registration trials. As it is not feasible to find an appropriate active control for the liquid HRV vaccine, it was agreed to by the regulatory authorities and GSK Biologicals to include placebo as a comparable control. The inclusion of placebo in this trial will allow the assessment of efficacy, safety and immunogenicity of the liquid HRV vaccine as compared to the placebo.

**Objectives**

**Primary**

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy is at least 10%.

**Secondary**

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid

HRV vaccine/placebo and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6 when co-administered with the routine childhood vaccines
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

**Study design**

- Experimental design: Phase III, double blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.
- Duration of the study: ***The subjects will be followed until April 2012 (i.e. end of RV season in China).*** The

intended duration of the study, per subject, will ***not exceed a maximum of 21 months***. The study will have a single epoch as follows. **Amended: 05 August 2011.**

– Primary: Primary starting Visit 1 (Day 0) and ending ***Visit 7 (April 2012 i.e. end of RV season in China)***. **Amended: 05 August 2011.**

Synopsis Table 1 presents study groups and epoch foreseen in the study.

**Synopsis Table 1 Study groups and epochs foreseen in the study**

| Group identifier | Number of subjects | Age (Min/Max) | Epochs |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 –16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedule: Two oral doses of the liquid HRV vaccine or placebo will be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.

  Subjects in each group will receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study must be documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (N = 1625)
  - Group Placebo (N = 1625)

The treatment groups for the study are presented in Synopsis Table 2.

**Synopsis Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine will be given concomitantly with liquid HRV vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

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- Treatment allocation: Randomised with balanced allocation (1:1).
- Blinding: Double-blind study.

Synopsis Table 3 presents blinding of study epoch.

**Synopsis Table 3 Blinding of study epochs**

| Study Epoch | Blinding |
|---|---|
| Primary | double-blind |

- Blood Sampling: Blood samples will be collected from two sub-cohorts of subjects.
  - Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).
  - Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) of liquid HRV vaccine/placebo after each dose, using diary cards (applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).
- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (applicable only for subjects in the immunogenicity sub-cohort 2).
- Unsolicited AEs will be followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV

vaccine/placebo.

- Recording of SAEs throughout the study period for all subjects.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.*** **Amended: 05 August 2011.**
- Active follow-up for occurrence of GE* episodes will be conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE is defined as diarrhoea with or without vomiting.
- For each GE episode occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after GE symptoms begin.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.*** **Amended: 05 August 2011.**
- ***All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).*** **Amended: 05 August 2011.**
- ***The additional informed consent will be taken for the extended follow-up.*** **Amended: 05 August 2011.**
- Type of study: self-contained
- Data collection: eCRF.
- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ***study conclusion***,

an annex report will present ***all*** data up to ***study conclusion***. **Amended: 05 August 2011.**

**Number of subjects** Target enrolment will be 3250 eligible subjects. (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

**Endpoint**

**Primary**

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).**Amended: 05 August 2011.**

**Secondary**

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***). **Amended: 05 August 2011.**

*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects).*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at

Visit 3 and seropositivity rate at Visit 6.

– Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as GMC at Visit 3 and at Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  - Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2

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of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AE** | Adverse event |
| **ATP** | According-To-Protocol |
| **$CCID_{50}$** | Median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells) |
| **CI** | Confidence Interval |
| **DMEM** | Dulbecco's Modified Eagle Medium |
| **DTPa** | Diphtheria, Tetanus, acellular Pertussis vaccine |
| **eCRF** | electronic Case Report Form |
| **$ED_{50}$** | Estimated dose 50% |
| **EL.U/mL** | ELISA Units per Millilitre |
| **ELISA** | Enzyme Linked Immunosorbent Assay |
| **EPI** | Expanded Program of Immunisation |
| **FHA** | Filamentous Haemagglutinin |
| **GCP** | Good Clinical Practice |
| **GE** | Gastroenteritis |
| **GMC** | Geometric Mean Concentration |
| **GSK** | GlaxoSmithKline |
| **GSM** | Global Study Manager |
| **HRV** | Human Rotavirus |
| **IB** | Investigator Brochure |
| **ICF** | Informed Consent Form |
| **ICH** | International Conference on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IgA** | Immunoglobulin A |
| **IM** | Intramuscular |
| **IND** | Investigational New Drug |
| **IRB** | Institutional Review Board |
| **IS** | Intussusception |
| **IU/mL** | International Units per Millilitre |
| **LAR** | Legally Acceptable Representative |
| **LSC** | Local Study Contact |
| **MedDRA** | Medical Dictionary for Regulatory Activities |

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| | |
|---|---|
| **Mg** | Milligram |
| **mL** | Millilitre |
| **MMWR** | Morbidity and Mortality Weekly Report |
| ***NIFDC*** | ***National Institute for Food and Drug Control*** |
| **O** | Oral |
| **OPV** | Oral Poliovirus vaccine |
| **PCR** | Polymerase Chain Reaction |
| **PRN** | Pertactin |
| **PT** | Pertussis toxid |
| **RV** | Rotavirus |
| **SAE** | Serious Adverse Event |
| **SAS** | Statistical Analysis System |
| **SBIR** | Internet Randomisation tool |
| **SDV** | Source Document Verification |
| **SPM** | Study Procedures Manual |
| **U/mL** | Units per Millilitre |
| **UA** | Upper Arm |
| **UMV** | Universal Mass Vaccination |
| **VE** | Vaccine Efficacy |
| **WHO** | World Health Organisation |

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# GLOSSARY OF TERMS

| | |
|---|---|
| **According-To-Protocol cohort:** | This cohort will include all subjects enrolled in the study who meet the criteria defined in the protocol for the considered analysis (Efficacy, immunogenicity, reactogenicity and safety). |
| **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.<br><br>An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. |
| **Blinding:** | A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event (SAE). |
| **Child in care:** | A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian. |
| **Diarrhoea:** | Passage of three or more looser than normal stools within a day. |
| **Eligible:** | Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria. |

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| | |
|---|---|
| **Epoch:** | An epoch is a well defined part of a protocol that covers a set of consecutive time-points. Generally, an epoch is self-contained and allows to perform a data analysis to address some of the trial objectives (e.g. primary, booster, yearly follow-ups). |
| **eTrack:** | GSK's tracking tool for clinical trials. |
| **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 6.7.1 and 10.4 for details on criteria for evaluability). |
| **Gastroenteritis:** | Diarrhoea with or without vomiting. |
| **Investigational vaccine/product:**<br><br>**(Synonym of Investigational Medicinal 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. |
| **Legally Acceptable Representative:** | ICH GCP defines Legally Accepted Representative (LAR) as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. |
| **Randomisation:** | Process of random attribution of treatment to subjects in order to reduce bias of selection. |
| **Serious adverse event:** | 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 event 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. |
| **Severe rotavirus gastroenteritis:** | An episode of rotavirus gastroenteritis with score ≥ 11 on a 20-point scoring system (Vesikari scoring system). |

| | |
|---|---|
| **Site Monitor:** | An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites. |
| **Solicited adverse event:** | AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject's parents/ LARs or an observer during a specified post-vaccination follow-up period. |
| **Sub-cohort:** | A group of subjects for whom specific data are collected compared to other subjects. |
| **Subject:** | Term used throughout the protocol to denote an individual whose parents/LARs have been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control. |
| **Subject number:** | A unique number identifying a subject, assigned to each subject consenting to participate in the study. |
| **Total vaccinated cohort:** | The total vaccinated cohort will include all subjects with at least one vaccine administration documented. A safety analysis based on the total vaccinated cohort will include all vaccinated subjects. An immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects for whom immunogenicity data are available. An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available. |
| **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:** | A number identifying a treatment to a subject, according to the study randomisation or treatment allocation. |
| **Unsolicited adverse event:** | Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE. |
| **Vomiting:** | One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day. |

# TRADEMARKS

The following trademarks are used in the present protocol.

**Note:** In the body of the Protocol (including the synopsis), the names of the vaccines will be written without the superscript symbol ™.

| Trademarks of the GlaxoSmithKline group of companies | Generic description |
|---|---|
| Rotarix™ | Human rotavirus vaccine |
| Infanrix™ | Combined diphtheria-tetanus-acellular pertussis (DTPa) vaccine |

| Trademarks not owned by the GlaxoSmithKline group of companies | Generic description |
|---|---|
| OPV (Institute of Medical Biology Chinese Academy of Medical Sciences') | Poliomyelitis (live) Vaccine (Monkey Kidney Cell), Oral |

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# 1. INTRODUCTION

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) among young children aged <5 years. A recent review estimated that RV is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year where the majority of the deaths occur in the developing countries in Asia and Africa [WHO, 2007]. In developed countries, RV infection rarely results in death but RV remains the most common cause of hospitalisation for GE in children and leads to major medical and societal costs [Glass, 1996].

Hospital-based surveillance performed in Asia indicates that 20 to 50% of hospitalisations for diarrhoea among children less than five years of age are associated with RV infection and the morbidity and mortality may be much higher than in previously estimated RV infections. RV infections occur in all children during the first few years of life, suggesting that the virus is not primarily transmitted through the oro-faecal route. Improved hygiene and sanitation therefore cannot alone result in decreased RV infections. RV infections frequently occur with vomiting, which can result in discontinuation of oral rehydration therapy. Although first infections can lead to disease that ranges from mild GE to severe or fatal diarrhoea with dehydration, they also can induce immunity against severe disease after reinfection. Based on these data, vaccines have been identified as the best current strategy to decrease the burden associated with severe and fatal RV diarrhoea [Kang, 2006].

China has the second largest birth cohort in the world and the second highest number of deaths due to RV infection. In China, RV is the most common cause of diarrhoea and an economic burden for the parents. Approximately 27, 000 RV associated deaths occur each year and 32% - 50% of the hospitalised diarrhoea are associated with an RV infection [Naghipour, 2008; Wang, 2009].

In a hospital based study in Shanghai, more than 80% of the children with RV infections were aged less than 2 years [Xu, 2008]. Since RV is the most important cause of acute GE, this large disease burden of RV GE in children points towards vaccination as an effective preventive measure. In China, introduction of a RV vaccine would most likely be beneficial for children and a significant proportion of the diarrhoeal disease burden might be prevented in the near future [Liu, 2006].

GlaxoSmithKline (GSK) Biologicals therefore has developed a human rotavirus (HRV) vaccine to meet this health need. GSK Biologicals' HRV vaccine is a monovalent vaccine based on a HRV strain 89-12 belonging to the serotype G1P1A and genotype [P8] originally obtained from the stool of a 15-month old infant with mild RV diarrhoea in Cincinnati, United States. GSK Biologicals has implemented several process changes to the 89-12 vaccine candidate to develop a lyophilised HRV vaccine containing RIX4414 cloned from 89-12 at passage 43 for oral administration after reconstitution with buffer. The parent 89-12 vaccine was well-tolerated, immunogenic and effective in preventing RV GE among vaccinated infants during a trial in the United States [Bernstein, 1998; Bernstein, 1999; Bernstein, 2002].

GSK Biologicals' lyophilised HRV vaccine has been extensively tested in clinical studies conducted in infants from Europe, North America, Latin America and the Caribbean, Asia and Africa. This vaccine was well-tolerated, immunogenic and efficacious against RV disease of any severity in infants [Vesikari, 2004; Vesikari, 2006]. Efficacy results from a subset (20,169 subjects) from the Latin American safety study followed for 9 to 10 months after Dose 2 of the vaccine demonstrated a high protection rate (85%) against severe RV GE and this rate reached 100% protection against the most severe RV GE (defined as GE with a Vesikari score of 19 or 20) [Ruiz Palacios, 2006]. Other large scale efficacy studies conducted in Europe confirmed the efficacy and cross-protection provided by the HRV vaccine [Vesikari, 2007].

## 1.1. Background

GSK Biologicals has also developed a liquid formulation of the HRV vaccine containing the same HRV strain (RIX4414), referred to as the "liquid HRV vaccine". Two doses of GSK Biologicals' liquid HRV vaccine have been evaluated and were as immunogenic as the lyophilised formulation in terms of anti-rotavirus Immunoglobulin A (IgA) antibody response. When co-administered with routine childhood vaccines including oral poliovirus vaccine (OPV), the liquid HRV vaccine was found to be immunogenic and similar to the lyophilised HRV vaccine. The liquid HRV vaccine is currently registered in ***at least 77 countries*** worldwide including Mexico, Brazil, Australia and the European Union. **Amended: 05 August 2011**

Please refer to the current Investigator Brochure for a review of the pre-clinical and clinical studies, and the potential risks and benefits of liquid HRV vaccine.

## 1.2. Rationale for the study and study design

As required by the regulatory guidelines for licensure of vaccines in China, phase III efficacy studies need to be conducted in China to generate local clinical data for submission of file for licensure in China.

The primary objective of this study is to evaluate the efficacy of the liquid HRV vaccine to prevent severe RV GE during the efficacy follow-up period. There will be an efficacy follow-up starting 2 weeks after the second dose of study vaccination till ***April 2012 (i.e. end of RV season in China).*** **Amended: 05 August 2011.**

GSK Biologicals also intends to submit immunogenicity and reactogenicity data of the liquid HRV vaccine and co-administered routine vaccines to the regulatory authorities. In order to assess the immunogenicity of the study vaccines, two immunogenicity sub-cohorts are planned to be enrolled into this study. Immunogenicity of the liquid HRV vaccine/placebo will be assessed in the first sub-cohort (N = 600). Immunogenicity of the co-administered routine vaccines and reactogenicity of the routine vaccines administered at Visit 1 and Visit 2 will be assessed in the second sub-cohort (N = 300). Reactogenicity of the liquid HRV vaccine/Placebo will be assessed in the whole cohort except immunogenicity second sub-cohort.

### 1.2.1. Rationale for the use of placebo

As per recommendations of the regulatory authorities in China, it is suggested to include a control group in vaccine registration trials. As it is not feasible to find an appropriate active control for the liquid HRV vaccine, it was agreed to by the regulatory authorities and GSK Biologicals to include placebo as a comparable control. The inclusion of placebo in this trial will allow the assessment of efficacy, safety and immunogenicity of the liquid HRV vaccine as compared to the placebo.

# 2. OBJECTIVES

## 2.1. Primary objective

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
  - Criteria: The primary objective will be reached if the lower limit of the 95% Confidence Interval (CI) on vaccine efficacy is at least 10%.

Refer to Section 10.1 for the definition of the primary endpoint.

## 2.2. Secondary objectives

*Efficacy*

- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe RV GE caused by non-G1 type of RV during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- To assess the efficacy of two doses of GSK Biologicals' liquid HRV vaccine against any and severe all cause GE during the efficacy follow-up period.

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*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300)*

- To assess the serum anti-rotavirus IgA antibody seroconversion rate of the HRV group as compared to the placebo group one month post Dose 2 of liquid HRV vaccine/placebo and seropositivity rate at Visit 6 when co-administered with the routine childhood vaccines.
- To assess the immunogenicity of GSK Biologicals' liquid HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month post Dose 2 of liquid HRV vaccine/placebo and at visit 6 when co-administered with the routine childhood vaccines
- To assess the effect of GSK Biologicals' liquid HRV vaccine on the immune response to all antigens contained in each of the co-administered childhood vaccines (Diphtheria, Tetanus, acellular Pertussis vaccine [DTPa] and Oral Poliovirus vaccine [OPV] vaccines).

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the liquid HRV vaccine/placebo in terms of occurrence of solicited adverse events (AEs).

*Subjects in the immunogenicity sub-cohort 2:*

- To assess the reactogenicity of the co-administered vaccines in terms of occurrence of solicited AEs when co-administered with the liquid HRV vaccine/placebo.

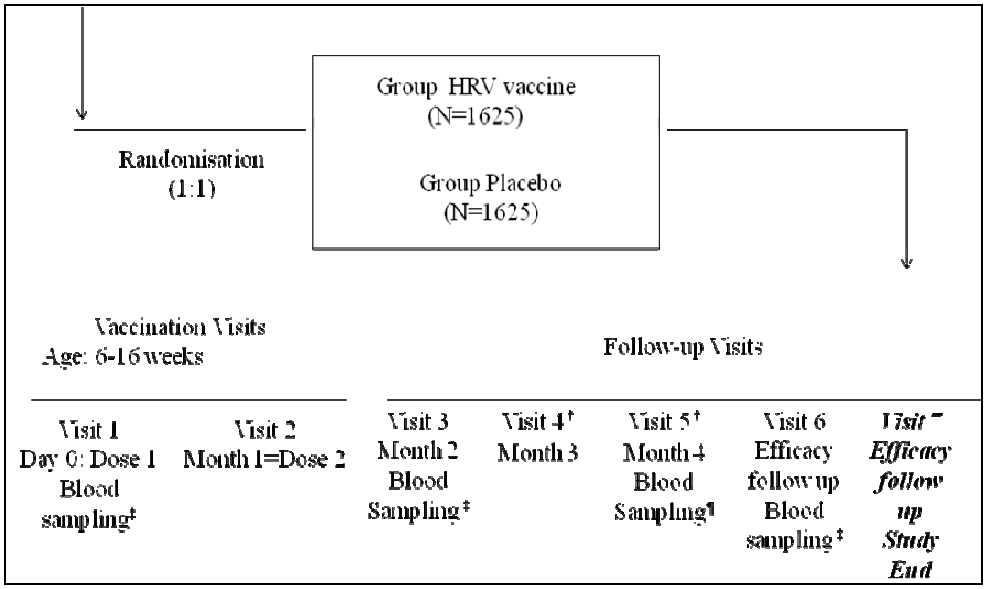
*All subjects:*

- To assess the safety of the liquid HRV vaccine in terms of unsolicited AEs and serious adverse events (SAEs).

Refer to Section 10.2 for the definition of the secondary endpoints.

# 3. STUDY DESIGN OVERVIEW

The study design for all subjects is as follows: **Amended: 05 August 2011.**




N: Number of subjects planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort2.
‡Blood will be drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood will be drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 will receive a dose of OPV at Visit 1, Visit 2 and Visit 3; and will receive a dose of DTPa at Visit 2, Visit 3 and Visit 4

- Experimental design: Phase III, double-blind, randomised, placebo controlled, multi-centric, single-country study with two parallel groups.

- Duration of the study: ***The subjects will be followed until April 2012 (i.e. end of RV season in China).*** The intended duration of the study, per subject, will ***not exceed a maximum of 21 months***. The study will have a single epoch as follows. **Amended: 05 August 2011.**

  – Primary: Primary starting Visit 1 (Day 0) and ending Visit *7* ***(April 2012 i.e. end of RV season in China)***. **Amended: 05 August 2011.**

Table 1 presents the study groups and the epoch foreseen in the study.

**Table 1 Study groups and epochs foreseen in the study**

| Study group | Number of subjects | Age in weeks (MIN/Max) | Epoch |
|---|---|---|---|
| | | | Primary |
| Group HRV vaccine | 1625 | 6 – 16 weeks | x |
| Group Placebo | 1625 | 6 – 16 weeks | x |

- Control: placebo control.
- Vaccination schedules: Two oral doses of the liquid HRV vaccine or placebo will be administered according to a 0, 1 month schedule to healthy infants aged 6 to 16 weeks at the time of Dose 1.
  - Subjects in each group will receive routine childhood vaccination according to the expanded program of immunisation (EPI) recommendations in China. Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All vaccines administered during the study must be documented in the electronic case report form (eCRF).
- Treatment groups:
  - Group HRV vaccine (N = 1625)
  - Group Placebo (N = 1625)

The treatment groups for the study are presented in Table 2.

**Table 2 Treatment groups**

| Treatment identifier | Vaccine name | Study Groups | |
|---|---|---|---|
| | | Group Placebo | Group HRV vaccine |
| 1 | liquid HRV vaccine | | x |
| 2 | Placebo | x | |
| 3 | DTPa * | x | x |
| 4 | OPV * | x | x |

*DTPa and OPV vaccine will be given concomitantly with liquid HRV Vaccine/placebo only for subjects in immunogenicity sub-cohort 2.

- Treatment allocation: Randomised with balanced allocation (1:1).

Refer to Section 5.2 for a detailed description of the randomisation method.

- Blinding**:** Double-blind study.

Refer to Section 5.3 for details of blinding procedure.

Table 3 presents the blinding of the study epoch.

**Table 3 Blinding of study epochs**

| Study Epochs | Blinding |
|---|---|
| Primary | double-blind |

Refer to Section 8.6 for details on when unblinding will be done.

- Blood Sampling: Blood samples will be collected from two sub-cohorts of subjects.

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600): Three blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo) and at Visit 6 (i.e. at approximately one year of age).

- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300): Four blood samples will be collected from the subjects. Blood samples will be drawn at Visit 1 (i.e. Day 0), at Visit 3 (i.e. one month post Dose 2 of liquid HRV vaccine/placebo), at Visit 5 (i.e. one month post Dose 3 of DTPa) and at Visit 6 (i.e. at approximately one year of age).

- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) of liquid HRV vaccine/placebo after each dose, using diary cards (applicable for all subjects excluding subjects in immunogenicity sub-cohort 2).

- Eight day (Day 0 – Day 7) follow-up period for solicited general AEs (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) of co-administered vaccines at Visit 1 (for OPV vaccine) and at Visit 2 (for OPV and DTPa vaccines) and for solicited local AEs (pain, swelling, redness) at Visit 2 (for DTPa vaccine), using diary cards (applicable only for subjects in the immunogenicity sub-cohort 2).

- Unsolicited AEs will be followed up for a period of 31 days (Day 0 – Day 30) after each dose of liquid HRV vaccine/placebo.

- Recording of SAEs throughout the study period for all subjects.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.*** **Amended: 05 August 2011.**

- Active follow-up for occurrence of GE* episodes will be conducted during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks).

  *Note: GE is defined as diarrhoea with or without vomiting.

- For each GE episode occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after GE symptoms begin.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.*** **Amended: 05 August 2011.**

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113808 (ROTA-075)
Amendment 2

- ***All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).*** **Amended: 05 August 2011.**

- ***The additional informed consent will be taken for the extended follow-up.*** **Amended: 05 August 2011.**

- Type of study: self-contained.

- Data collection: eCRF .

- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ***study conclusion***, an annex report will present ***all*** data up to ***study conclusion***. **Amended: 05 August 2011.**

# 4. STUDY COHORT

## 4.1. Number of subjects/centres

Target enrolment will be 3250 eligible subjects. (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

Refer to Section 10.3 for a detailed description of the criteria used in the estimation of the sample size.

Table 4 presents the sub-cohorts in the study.

**Table 4 Sub-cohorts**

| Sub-cohort name | Description | Estimated number of subjects |
|---|---|---|
| Immunogenicity Sub-cohort 1 | To assess the immunogenicity of the liquid HRV vaccine/placebo.<br>To assess the reactogenicity of the liquid HRV vaccine/placebo.<br>To assess the safety (unsolicited AEs and SAEs) of the liquid HRV/placebo | 600 |
| Immunogenicity Sub-cohort 2 | To assess the immunogenicity of the liquid HRV vaccine/placebo as well as the routine childhood vaccines (i.e. OPV and DTPa).<br>To assess the reactogenicity of OPV and DTPa only at Visit 1 and Visit 2.<br>To assess the safety (unsolicited AEs and SAEs) of the liquid HRV/placebo<br>Reactogenicity of the liquid HRV vaccine/placebo will not be assessed | 300 |

Overview of the recruitment plan

- Enrolment will be terminated when 3250 eligible subjects have been enrolled.
- All enrolled subjects will be followed for efficacy and safety.
- The intended duration of the study, per subject, will ***not exceed a maximum of 21 months***. **Amended: 05 August 2011.**
- The recruitment will be monitored by Internet Randomisation tool (SBIR).

## 4.2. Inclusion criteria for enrolment

All subjects must satisfy ALL the following criteria at study entry:

- Subjects who the investigator believes that their parents/Legally Acceptable Representatives (LARs) can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.
- Written informed consent obtained from the parents/LARs of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of 36 to 42 weeks inclusive.

## 4.3. Exclusion criteria for enrolment

The following criteria should be checked at the time of study entry. If **ANY** exclusion criterion applies, the subject must not be included in the study:

- Child in care.

  Refer to the GLOSSARY OF TERMS for the definition of child in care.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone 0.5 mg/kg/day, or equivalent, inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine not foreseen by the study protocol within 14 days before each dose of study vaccines and ending 14 days after.of the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.
- 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).
- Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for Intussusception (IS).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness.
- History of confirmed RV GE.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature (37.1°C on axillary setting as defined by the Chinese authorities.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).
- GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).

- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

In addition to the criteria mentioned above, the following criteria will be applicable to all subjects in the immunogenicity sub-cohort 2:

- History of diphtheria, tetanus and pertussis disease.
- History of seizures or progressive neurological disease.
- Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

# 5. CONDUCT OF THE STUDY

## 5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject's parents/LARs informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written informed consent must be obtained from each subject's parent(s)/LAR(s), prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to 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 local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

## 5.2. Subject identification and randomisation of treatment

The target will be to enrol 3250 eligible subjects to be randomly assigned to two study groups in a balanced (1:1) ratio (1625 subjects in each group) to obtain a total of 2600 evaluable subjects (1300 subjects in each group).

### 5.2.1. 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.

### 5.2.2. Randomisation of treatment

#### 5.2.2.1. Randomisation of supplies

The randomisation will be performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS® ) (Cary, NC, USA) by GSK Biologicals.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, a 6%-over-randomisation of supplies will be prepared.

The vaccine doses will be distributed to the study centres while respecting the randomisation block size.

#### 5.2.2.2. Treatment allocation to the subject

The treatment allocation at the investigator site will be performed using SBIR. The treatment numbers will be allocated by kit. The randomisation algorithm will use a minimisation procedure accounting for centre.

When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

After having checked the eligibility of the subject and obtaining the ICF, the site staff in charge of the vaccination will access SBIR. Upon providing the subject identification

number, the randomisation system will use the minimisation algorithm to determine the treatment number to be used for the subject. Each treatment number must be recorded in the eCRF on the Vaccine Administration screen.

### 5.2.3. Randomisation of subjects to assay sub-cohorts

Randomisation for all the sub-cohorts will be done in parallel Blood samples will be collected from both the sub-cohorts of subjects:

- Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).
- Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300).

## 5.3. Method of blinding

The study will be conducted in a double-blind manner with respect to the liquid HRV vaccine and placebo. The parents/LARs of the subjects, the study personnel and the investigator will be unaware of the study vaccine administered (liquid HRV vaccine/Placebo).

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 SAE.

If the final analysis will be done by an independent analysis centre in order to preserve blinding as much as possible, when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period, access to the individual treatment decode during the final analysis will be limited to the statistician and the database administrator to maintain double blinding until study end. This will allow unbiased evaluation of the study vaccine.

The serological data, which would lead to the unblinding of the treatment groups, will not be available during the course of the study to any investigator or any person involved in the clinical conduct of the study (including data cleaning).

## 5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

### 5.4.1. Routine vaccinations

Subjects in the immunogenicity sub-cohort 2 will receive DTPa and OPV vaccines concomitantly with the liquid HRV vaccine/placebo dose. All other subjects will receive

routine childhood vaccinations according to the local immunisation practice. Administration of all routine childhood vaccinations since birth must be documented in the eCRF.

### 5.4.2. Follow-up of GE cases

Parents/LARs of all subjects will be instructed to collect a stool sample from the subject if the subject develops GE symptoms (defined as diarrhoea with or without vomiting) during the study period starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks). A GE stool sample should be collected as soon as possible after the illness begins. A second GE stool sample is to be collected if the first sample was insufficient. A stool sample should be collected for each GE episode. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes.

For each suspected GE episode occurring during the study period, a GE diary card should be completed by the parents/LARs daily until end of the GE symptoms. The completed diary cards should be returned to the investigator at the following study visit. The investigator will verify the returned completed GE diary cards and he or the study personnel will transcribe the information into the appropriate sections of the eCRF, in English.

### 5.4.3. Standard of Care

All subjects will undergo a general physical examination. If during the study, the investigator discovers any underlying medical condition, the subject will be referred to the local healthcare system.

## 5.5. Outline of study procedures

Table 5 presents the list of study procedures.

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**Table 5 List of study procedures (Amended: 05 August 2011)**

| **Age** | **6 to 16 weeks** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Epoch** | **Primary** | | | | | **Efficacy follow-up** | |
| **Type of contact** | **visit 1** | **visit 2** | **visit 3** | **visit 4 *** | **visit 5 *** | **visit 6** | ***Visit 7*** |
| **Time-points** | **days 0** | **months 1** | **months 2** | **months 3** | **months 4** | ***years* 1 of age** | ***April 2012[β]*** |
| **Sampling time-points** | **Pre-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Efficacy follow up** | ***Efficacy follow up*** |
| Informed consent | ● | | | | | | |
| ***Re-consenting for Visit 7 follow-up*** | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | O | O | O | O | O | O |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approxi-mately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 2) | ● (Approxima-tely 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+DTPa) | ● (OPV+DTPa) | ● (DTPa) | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of ***unsolicited AEs*** within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | visit 1 | visit 2 | visit 3 | visit 4 * | visit 5 * | visit 6 | *Visit 7* |
| Time-points | days 0 | months 1 | months 2 | months 3 | months 4 | *years* 1 of age | *April 2012*[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | *Efficacy follow up* |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | O | O | O | O | O | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
***[β]i.e. end of the RV season in China. Amended: 05 August 2011***

Table 6 presents the intervals between study visits.

**Table 6 Intervals between study visits (Amended: 05 August 2011)**

| Interval | Optimal length of interval [1] | Maximum interval allowed [2] |
|---|---|---|
| 1 (Visit 1)→(Visit 2) | 30-48 days | 21-48 days |
| 2 ((Visit 2)→(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3)→(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | ***1 year of age± 2 weeks[γ]*** | ***1 year of age ± 30 days*** |
| ***6 (Visit 6) → (Visit 7)*** | ***01 April 2012 to 30 April 2012[γ]*** | ***01 April 2012 to 31 May 2012*** |

[1]. Whenever possible the investigator should arrange study visits within this interval
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they make the study visit outside this interval
***[γ]It is a defined time point for follow up visit in a range and not an interval. Amended: 05 August 2011***
Note: The date of the previous visit serves as the reference date for intervals between study visits. Refer to section 3 for details on the study visits applicable to the subjects in the study.

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## 5.6. Detailed description of study procedures

### 5.6.1. Procedures prior to study participation

#### 5.6.1.1. Informed consent

Before performing any other study procedure, the signed/thumb printed informed consent of the subject's parents/LARs needs to be obtained. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

### 5.6.2. Procedures prior to the first vaccination

#### 5.6.2.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

#### 5.6.2.2. Collect demographic data

Record demographic data such as date of birth, gender, race in the subject's eCRF.

#### 5.6.2.3. Collect gestational age

Gestational age of the subject needs to be collected and recorded in the eCRF.

#### 5.6.2.4. Medical history

Perform a history-directed medical examination and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

#### 5.6.2.5. Physical examination

Perform a physical examination of the subject, including assessment of body temperature, height and weight. Collected information needs to be recorded in the eCRF.

#### 5.6.2.6. Blood sampling for antibody determination

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

During Visit 1 a volume of approximately 3 mL of whole blood to get a serum volume of 1.5 mL will be drawn from subjects belonging to immunogenicity sub-cohort 1 and a volume of approximately 4.5 mL of whole blood to get a serum volume of 2 mL will be

drawn from subjects belonging to immunogenicity sub-cohort 2 included in the immunogenicity sub-cohort for each analysis of humoral immune response at each pre-defined time-point. After centrifugation, serum samples should be kept at –20°C until shipment.

### 5.6.3. Procedures during the primary epoch

#### 5.6.3.1. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant vaccination must be recorded in the eCRF as described in Section 6.7. Refer also to Section 6.7for details on the medication/vaccination forbidden and/or allowed during the study.

At each study visit subsequent to the first vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition listed in Section 6.8. If it is the case, the condition(s) must be recorded in the eCRF.

#### 5.6.3.2. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination are to be checked at Visit 1 and Visit 2. Refer to Section 6.5and 6.6.

#### 5.6.3.3. Pre-vaccination body temperature / Assess pre-vaccination body temperature

The axillary body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be axillary. If the subject has fever (Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.), the vaccination visit will be rescheduled within the interval for this visit (see Table 5).

#### 5.6.3.4. Randomisation

At the first vaccination visit, randomisation will occur as explained in Section 5.2.

#### 5.6.3.5. Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis

Information regarding previous vaccination of subjects with diphtheria, tetanus, pertussis and poliomyelitis needs to be recorded in eCRF.

#### 5.6.3.6. Blood sampling for antibody determination

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

A volume of approximately 3 mL of whole blood to get a serum volume of 1.5 mL will be drawn from subjects belonging immunogenicity sub-cohort 1 and 2 during Visit 3. During Visit 5, a volume of approximately 3 mL of blood get a serum volume of 1.5 mL will be drawn only from subjects in immunogenicity sub-cohort 2 included in the immunogenicity sub-cohort for each analysis of humoral immune response at each pre-defined time-point. After centrifugation, serum samples should be kept at –20°C until shipment.

#### 5.6.3.7. Treatment number assignment

At the first vaccination visit, the subject will be assigned a treatment number defining the treatment he/she will be receiving. The treatment number must be recorded in the eCRF at each vaccination visit.

#### 5.6.3.8. Vaccination

After completing the pre-requisite procedures prior to vaccination, one dose of study vaccine (liquid HRV vaccine) or placebo will be administered orally (refer to Section 6 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit. The subjects will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccines.

#### 5.6.3.9. Recording of co-administered vaccines in sub-cohort 2

The co-administered vaccines in sub-cohort 2 (OPV and DTPa vaccine) will be recorded as and when administered by the investigator in eCRF.

#### 5.6.3.10. Daily post-vaccination recording of solicited general adverse events after each dose of vaccines/ placebo given.

- Refer to Section 8.3 for procedures for the Investigator to record AEs and SAEs that are related to study participation or GSK concomitant medication/vaccination and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.

- The subjects' parents/LARs will be instructed to contact the investigator immediately should the subjects manifest any signs or symptoms parents/LARs perceive as serious.

- After each dose of liquid HRV vaccine/placebo, diary cards will be provided to the subjects parents/LARs to record body (axillary) temperature and any solicited general AEs daily (i.e. on the day of vaccination and during the next 7 days) occurring within 8 days of liquid HRV/ placebo vaccination. This procedure will be done for all subjects except for subjects in immunogenicity sub-cohort 2.

- After Dose 1 and Dose 2 of OPV, diary cards will be provided to the subjects parents/LARs to record body (axillary) temperature and any solicited general AEs daily (i.e. on the day of vaccination and during the next 7 days) occurring within 8 days of OPV vaccination. This procedure will be followed only for subjects in immunogenicity sub-cohort 2.

- After Dose 1 of DTPa vaccine, diary cards will be provided to the subjects parents/LARs to record body (axillary) temperature and any solicited local and general AEs daily (i.e. on the day of vaccination and during the next 7 days) occurring within 8 days of DTPa vaccination. This procedure will be followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.11. Recording of serious and non-serious adverse events

- Refer to Section 8.3 for procedures for the investigator to record AEs and SAEs that are related to study participation or GSK concomitant medication/vaccination and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.

- The subjects' parents/LARs will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

- At each visit, diary cards will be provided to the subjects' parents/LARs to record body (axillary) temperature and any SAEs occurring during visit intervals until the next visit. This procedure of recording serious AEs will be done throughout the study (after first vaccine dose till study end). The parents/LARs will be instructed to return the completed diary card to the Investigator at the next visit.

- Any non serious AEs occurring within 31 days (Day 0 – 30) post vaccination will be recorded by the investigator in eCRF.

#### 5.6.3.12. Recording GE occurring throughout the study period in a GE diary card

At each visit, GE diary cards will be provided to the subject's parents/LARs to record any GE episodes occurring after vaccination and during visit intervals. The GE diary card should be completed by the parents/LARs daily until end of the GE symptoms. The parents/LARs will be instructed to return the completed diary card to the Investigator at the next visit.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.13. Collection of stool samples in case the child develops GE

As specified in the List of Study Procedures in Section 5.5 (Table 5), Parents/LARs of all subjects will be instructed to collect a stool sample from the subject if the subject develops GE symptoms (defined as diarrhoea with or without vomiting) during the course of the study starting from Dose 1 up to the last visit planned for the subject via telephone contact or by other means (at least every 2 weeks). A GE stool sample should be collected as soon as possible after the illness begins. A second GE stool sample is to be collected if the first sample was insufficient. A stool sample should be collected for each GE episode. Two occurrences of diarrhoea will be classified as separate episodes if there will be five or more diarrhoea-free days between the episodes. Samples should be transferred rapidly to the investigator's laboratory or investigator's site (within 0 to 3 days).

Refer to the Module on Biospecimen Management in the SPM for general handling of stool samples.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.14. Return of diary cards and GE diary cards

The completed diary cards and GE diary cards will be collected and verified during discussion with the subject's parents/LARs at the subsequent visit. Any unreturned GE diary cards will be sought from the subject's parents/LARs through a convenient procedure.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

#### 5.6.3.15. Diary card and GE diary card transcription by investigator

The investigator will transcribe the information collected from diary cards and GE diary cards into the eCRF in English.

This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.
**Amended: 05 August 2011.**

On Visit 4 and Visit 5, this procedure is followed only for subjects in immunogenicity sub-cohort 2.

### *5.6.4.* Procedures during Efficacy follow-up *(Visit 6)*

***For subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2:***

***The additional consent will be obtained from the subject's parents/LARs. Retrospective data on intercurrent medical condition, concomitant medication/vaccination, GE episodes and SAEs will also be collected.***

***For subjects who are returning for Visit 6 after the implementation of protocol amendment 2:***

Note that some of the procedures to be performed during the follow-up visits (such as physical examination, blood sampling, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of ***S***AEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11. ***For the participation in the extended follow-up till Visit 7, additional consent of subject's parents/LARs will be obtained.*** **Amended: 05 August 2011.**

#### 5.6.4.1. Blood sampling for antibody determination

As specified in the List of Study Procedures in Section 5.5 (Table 5), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

A volume of approximately 3 mL of whole blood to get a serum volume of 1.5 mL will be drawn from subjects in immunogenicity sub-cohort 1 and 2 during Visit 6 included in the immunogenicity sub-cohort for each analysis of humoral immune response at each pre-defined time-point. After centrifugation, serum samples should be kept at –20°C until shipment.

### *5.6.5. Procedures during Efficacy follow-up (Visit 7)*

***Note that some of the procedures to be performed during the follow-up visits (such as physical examination, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of SAEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11.*** **Amended: 05 August 2011.**

#### 5.6.5.1. Study conclusion

The investigator will review all the data collected to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

At study conclusion, post-trial commercial vaccines will not be provided to the subjects.

## 5.7. Biological sample handling and analysis

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

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

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccines and its constituents or the disease under study to allow to achieve a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the subject's parent(s)/LAR(s).

Any human pharmacogenetic testing will require specific consent from the individual subject's parents/LARs and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendments.

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

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

### 5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals or GSK designated laboratory (such as a central laboratory), it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the According-To-Protocol (ATP) analysis (See Section 10.4 for the definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to the Module on Clinical Trial Supplies in the SPM.

### 5.7.2. Biological samples

Table 7 presents the biological samples used in this study.

**Table 7 Biological samples (Amended: 05 August 2011)**

| Sample type | Quantity | Unit | Time-point | Sub-cohort Name* |
|---|---|---|---|---|
| Blood | Approximately 3 | ml | Schedule (Visit 1) days 0 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 4.5 | ml | Schedule (Visit 1) days 0 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) months 2 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) months 2 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 5) months 4 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) years 1 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) years 1 | Immunogenicity Sub-cohort 2 |
| Stool | NA | NA | Schedule From Visit 1 (Days 0) to Visit ***7 (April 2012)***[β] | All subjects |

*Refer to Section 5.2.3 for sub-cohort description.
NA=Not applicable
[β] ***i.e. end of RV season in China.*** **Amended: 05 August 2011**

### 5.7.3. Laboratory assays

**GE Stool analysis**

All stool samples collected during the study will be shipped frozen to a GSK Biologicals designated laboratory in China where aliquots will be prepared to be sent to a qualified lab and to GSK Biologicals, Belgium (or sponsor designated laboratory), for back-up. The tests in the laboratory at GSK Biologicals, Belgium will be performed only if necessary.

All GE stool samples will be analysed by Enzyme Linked Immunosorbent Assay (ELISA) for detection of RV antigen. If a stool sample tests positive for RV antigen, the sample will be tested by Polymerase Chain Reaction (PCR) to determine the G and P genotype. If any RV G1 strain is detected in the stool specimens from Visit 1 up to study end, viral strain of the vaccine will be differentiated from the wild type strain by sequence analysis or an equivalent approach.

**Serum analysis**

All serum samples collected during the study will be shipped frozen to a GSK Biologicals designated laboratory in China where aliquots will be prepared to be sent to a qualified lab and to GSK Biologicals, Belgium (or sponsor designated laboratory), for back-up, if necessary.

Serum anti-rotavirus IgA antibody concentrations will be measured in all serum samples collected at Visit 1, Visit 3 and Visit 6 using ELISA. The assay cut-off is 20 U/mL. Antibodies to all antigens contained in the co-administered vaccines will be measured at Visit 1 and Visit 5 (applicable only for subjects in the immunogenicity sub-cohort 2).

The laboratory assays to be performed are presented in Table 8.

**Table 8 Laboratory Assays Amended: 05 August 2011**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | GSK Biologicals* |
| Serum | anti-diphtheria | ELISA** | ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-tetanus | ELISA** | ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-PT | ELISA** | ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-FHA | ELISA** | ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-PRN | ELISA** | ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | ***NIFDC*** | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | ***NIFDC*** | $ED_{50}$† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | ***NIFDC*** | $ED_{50}$† | 1:8 | GSK Biologicals* |

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals in China.
**or Multiplex
ELISA = Enzyme Linked Immunosorbent Assay
***NIFDC*** = National Institute for ***Food and Drug Control*** **Amended: 05 August 2011**
U = Units; IU = International Units; EL.U = Elisa Units
†$ED_{50}$ = Estimated dose 50% is the seroprotective level.

Collected samples will be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

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

## 5.7.4. Biological samples evaluation

### 5.7.4.1. Immunological read-outs

**Table 9 Immunological read-outs (Amended: 05 August 2011)**

| Blood sampling time-point | | Sub-cohort Name | No.of subjects | Component | Components priority rank |
|---|---|---|---|---|---|
| Type of contact and time-point | Sampling time-point | | | | |
| Visit 1 (days 0) | Pre-Vacc | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 1 0) | Pre-Vacc | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 3 2) | Post-Vacc § | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 3 (2) | Post-Vacc § | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| Visit 5 months 4) | Post-Vacc * | Immunogenicity Sub-cohort 2 | 300 | Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 6 1) | Efficacy follow up | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 6 (years 1) | Efficacy follow up | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| **GE stool analysis** | | | | | |
| Visit 1 (Days 0) to Visit ***7 (April 2012)***$^{\beta}$ | Throughout the study period | All subjects | | RV antigen | None |

D = Diphtheria, T = Tetanus
§ Post-Vacc 2: One month post Dose 2 of liquid HRV vaccine/placebo
*Post-Vacc 3: Two month post Dose 3 of OPV and one month post of Dose 3 of DTPa
$^{\beta}$ ***i.e. end of RV season in China.*** **Amended: 05 August 2011**

**Additional analysis**

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

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 9.

### 5.7.5. Immunological correlates of protection

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

Antibodies against the pertussis components PT, FHA and PRN will be measured by an ELISA technique developed by National Institute for the Control of Pharmaceutical and Biological Products (NICPBP). Purified pertussis antigens and references of anti-pertussis antibodies will be provided by GSK Biologicals. The cut-off of the test will be set at 5 ELISA units per ml (EL.U/ml). As per Chinese regulatory requirements, the clinical cut-off (vaccine response) for anti-PT and anti-FHA is defined at ≥20 EL.U/ml. The response to PRN is evaluated via the calculation of at least a 4-fold increase in antibody concentrations from pre to post- vaccination. No serological correlate of protection against pertussis has been established [Granström, 1987; Karpinsky, 1987]. Therefore seropositivity and vaccine response rates are used to evaluate vaccine immunogenicity. Subjects with antibody concentration below the cut-off of 5 EL.U/ml are considered seronegative.

## 6. STUDY VACCINES AND ADMINISTRATION

### 6.1. Description of study vaccines

The liquid HRV vaccine and placebo to be used in this study have been developed and manufactured by GSK Biologicals.

The DTPa vaccine to be used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 has been developed and manufactured by GSK Biologicals.

The OPV vaccine to be used in this study as concomitant vaccine for subjects in immunogenicity sub-cohort 2 has been developed and manufactured by Institute of Medical Biology Chinese Academy of Medical Sciences.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

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

Table 10 presents the formulation and presentation of study vaccines.

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**Table 10 Study vaccines**

| Vaccine Name | Treatment identifier | Formulation | Presentation | Volume |
|---|---|---|---|---|
| liquid HRV vaccine | Treatment 1 | RIX4414 HRV strain at least $10^{6.0}$ median $CCID_{50}$ Di-sodium Adipate 132.74 mg<br>DMEM 2.26 mg<br>Sucrose 48.8% (w/w)<br>water for injection q.s. as 1.5 mL | Liquid in a pre-filled oral applicator | 1.5 mL |
| Placebo | Treatment 2 | Di-sodium Adipate 132.74 mg<br>DMEM 2.26 mg<br>Sucrose 48.8% (w/w)<br>water for injection q.s. as 1.5 mL | Liquid in a pre-filled oral applicator | 1.5 mL |
| DTPa | Treatment3 | Diphtheria toxoid ≥ 30 international units (IU) 25 Limits of flocculation (Lf) Tetanus toxoid ≥ 40 IU (10Lf) Pertussis toxoid 25 µg Filamentous haemagglutinin 25 µg Pertactin 8 µg Aluminium as salts 0.5 mg 2-phenoxyethanol ≤ 2.5 mg | Turbid white suspension in a pre-filled syringe | 0.5 mL |
| OPV | Treatment4 | per 0.1ml(2 drops) Total polio-virus, not less than 6.15lgCCID50<br>type1, not less than 6.0 lgCCID50<br>type2, not less than 5.0 lgCCID50<br>type3, not less than 5.5 lgCCID50 | liquid, oral | 1 mL/vial (2drops/dose) (10dose/vial) |

$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)
DMEM = Dulbecco's Modified Eagle Medium

## 6.2. Storage and handling of study vaccines

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

The study vaccines must be stored at the defined temperature range (i.e. +2 to +8°C). Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines. The storage temperature of the vaccines will be monitored daily with temperature monitoring device(s) (at the minimum calibrated) and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation, i.e. temperature outside the range (0-8°C of storage), must be reported to the sponsor as soon as detected. Following an exposure to such a temperature deviation, vaccines will not be used until approval has been given by the Sponsor.

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In case of temperature deviation between 0 and +2°C, the impacted study vaccines can still be administered, but the site must take adequate actions to go back to defined range +2 to +8°C and avoid re-occurrence of such a temperature deviation.

Please refer to the Module on Clinical Trial Supplies in the SPM for more details on the Temperature deviation process and the Module on Clinical Trial Supplies for details and instructions on the packaging and accountability of the study vaccines.

## 6.3. Dosage and administration of study vaccines

The pre-filled oral applicator is shaken well before use. The product (vaccine or placebo) should then be administered smoothly as a single oral dose.

In order to allow swallowing of the entire volume of the single oral dose, the administration should occur in a quiet environment. Sufficient time should be allowed for the baby to swallow the liquid vaccine solution, to avoid regurgitation or vomiting. Should however the subject regurgitate or vomit after study vaccine administration, no new study vaccine dose should be administered. The subject may continue to participate in the study. The oral vaccine intake characteristics (smooth vaccine intake, vaccine intake interrupted due to coughing or choking, regurgitation after vaccine intake, vomiting after vaccine intake) should be recorded in the eCRF.

The vaccination regimen is summarised in Table 11.

**Table 11 Dosage and administration**

| Type of contact and time-point | Doses | Treatment Group | Vaccine | Route [1] | Site [2] | Side [3] |
|---|---|---|---|---|---|---|
| Visit 1 (days 0); Visit 2 months 1) | 1 | Group HRV vaccine | liquid HRV vaccine | O | | |
| Visit 1 days 0); Visit 2 months 1 | 1 | Group Placebo | Placebo | O | | |
| Visit 2 months 1; Visit 3 months 2); Visit 4 months 3) | 1 | Group HRV vaccine<br>Group Placebo | DTPa | IM | Ant T | L |
| Visit 1 days 0); Visit 2 months 1; Visit 3 months 2) | 1 | Group HRV vaccine<br>Group Placebo | OPV | O | | |

[1]Oral (O)/ Intramuscular (IM)
[2]Thigh (T): Anterolateral (Ant)
[3]Left (L)

## 6.4. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see the Module on Clinical Trial Supplies in the SPM for details).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 6% additional doses will be supplied to replace those that are unusable.

The investigator will use the SBIR to obtain the replacement vial number. The replacement numbers will be allocated by component. The system will ensure, in a blinded manner, that the replacement vial is of the same formulation as the randomised vaccine.

## 6.5. Contraindications to subsequent vaccination

***GSK Biologicals' liquid HRV vaccine or placebo:***

The following events constitute absolute contraindications to further administration of the liquid HRV vaccine or placebo. If any of these events occur during the study, the subject must not receive additional doses of the vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4.4).

- Hypersensitivity reaction following the administration of the liquid HRV vaccine or placebo.

- IS and any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

The following events constitute contraindications to administration of liquid HRV vaccine and placebo at that point in time; if any of these events occur 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.

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. (Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.) All vaccines can be administered to persons with a minor illness such as mild upper respiratory infection with or without low-grade febrile illness.

- GE within 7 days preceding the study vaccine administration.

***GSK Biologicals' DTPa vaccine:***

- DTPa vaccine should not be administered to subjects with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of DTPa vaccine.

- DTPa vaccine is contra-indicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances the vaccination course should be continued with diphtheria and tetanus vaccine.

## 6.6. Warnings and precautions

Warnings and precautions related to the liquid HRV vaccine

The liquid HRV vaccine should under no circumstances be injected

Warnings and precautions related to the DTPa.

It is good clinical practice that immunisation should be preceded by a review of the medical history (especially with regard to previous immunisation and possible occurrence of undesirable events) and a clinical examination.

As with other vaccines, the administration of DTPa vaccine should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contra-indication.

If any of the following events occur in temporal relation to receipt of DTPa, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks, particularly since these events are not associated with permanent sequelae.

The following events were previously considered contra-indications for Diphtheria Tetanus whole cell Pertussis (DTPw) and can now be considered general precautions:

- Temperature of ≥ 40.5°C within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

A history of febrile convulsions and a family history of convulsive fits do not constitute contra-indications.

HIV infection is not considered as a contra-indication.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

For this reason, the vaccinee should remain under medical supervision for 30 minutes after immunisation.

As for all diphtheria, tetanus and pertussis vaccines, the vaccine should be given deep intramuscularly and preferably at alternate injection sites.

DTPa vaccine should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

DTPa vaccine should under no circumstances be administered intravenously.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

For warnings and precautions related to the OPV vaccines, please refer to the respective product labels/package inserts.

## 6.7. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject's parents/LARs about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, are to be recorded in the eCRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

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 and any other symptom, to prevent fever from occurring (Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities.).

Similarly, concomitant medication administered for the treatment of a SAE, at any time, must be recorded on the SAE screens in the eCRF. Refer to Section 8.1.2 for the definition of a SAE.

### 6.7.1. Medications/products that may lead to the elimination of a subject from ATP analyses

The following criteria should be checked at each visit subsequent to the first vaccination 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 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 vaccines during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. For corticosteroids, this will mean prednisone 0.5 mg/kg/day, or equivalent. Inhaled and 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 the liquid HRV vaccine/placebo and ending 14 days after, with the exception of routine childhood vaccinations.
- Administration of immunoglobulins and/or any blood products during the study period.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).

### 6.7.2. Time window for recording concomitant medication/vaccination in the eCRF

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with the administration of each dose of study vaccine and ending 31 days after each dose of study vaccine must be recorded in the eCRF.

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding each dose of study vaccine must be recorded in the eCRF.

Any investigational medication or vaccine administered throughout the study (i.e. from Day 0 through Day 30 must be recorded in the eCRF.

***All medications given for the protocol defined GE episode that occur during the period starting with the administration of each dose of study vaccine and ending 31 days after each dose of study vaccine must be recorded both in the concomitant medication section of the eCRF and in the respective GE section of the eCRF. The medications given for the protocol defined GE episode occurring outside the window of 31 days post vaccination must be recorded only in the respective GE section of the eCRF.***
**Amended: 05 August 2011.**

### 6.8. Intercurrent medical conditions that may lead to elimination from an ATP cohort

Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition likely to alter the immune response or are confirmed to have an immunodeficiency condition.

## 7. HEALTH ECONOMICS

Not applicable.

## 8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

Each subject's parents/LARs will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

### 8.1. Safety definitions

#### 8.1.1. Definition of an adverse event

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

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

**Examples of an AE include:**

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- 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 liquid HRV vaccine administration even though they 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 procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).

- 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.

- For therapeutic studies, 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).

NB AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

### 8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death.

b. Is life-threatening.

   NB: 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, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation.

   NB: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have

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been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, or

NB: 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 like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

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.

### 8.1.3. Solicited adverse events

The following general AEs presented in Table 12 will be solicited after administration of each liquid HRV vaccine/placebo in all subjects excluding subjects in immunogenicity sub-cohort 2:

**Table 12 Solicited general adverse events for liquid HRV vaccine/placebo (excluding subjects in immunogenicity sub-cohort 2)**

| |
|---|
| Cough/runny nose |
| Fever* |
| Irritability/Fussiness |
| Loss of appetite |
| Vomiting |
| Diarrhoea |

*(Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities)

The following general AEs presented in Table 13 will be solicited only for subjects in the immunogenicity sub-cohort 2:

**Table 13 Solicited general adverse events for co-administered childhood vaccines**

| |
|---|
| Fever* |
| Irritability/Fussiness |
| Loss of appetite |
| Drowsiness |
| Gastrointestinal symptoms† |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain. These AEs are specific to OPV.

*(Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities).

NB Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

The following local AEs presented in Table 14 will be solicited only for subjects in the immunogenicity sub-cohort 2:

**Table 14 Solicited local adverse events for DTPa**

| |
|---|
| Pain at injection site |
| Redness at injection site |
| Swelling at injection site |

### 8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. vital signs) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

## 8.2. Events or outcomes not qualifying as adverse events or serious adverse events

Not applicable.

## 8.3. Detecting and recording adverse events, serious adverse events

### 8.3.1. Time period for detecting and recording adverse events, serious adverse events

All AEs starting within 31days following administration of each dose of study vaccine must be recorded into the AE screen in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will be done throughout the study period for each subject. See Section 8.4 for instructions on reporting and recording SAEs.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 15.

**Table 15 Reporting periods for adverse events, serious adverse events (Amended: 05 August 2011)**

| Study activity | Pre-Vacc* | V1 Dose 1 | 7 days post-vacc | 30 days post-vacc | V2 Dose 2 | 7 days post-vacc | 30 days post-vacc | V3 | V4 | V5 | V6 | *Study Conclusion V7* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D0 | | | M1 | | | M2 | M3 | M4 | Approximately One year of age | *April 2012*[β] |
| Reporting of solicited local and/or general AEs† | | | | | | | | | | | | |
| Reporting of unsolicited AEs | | | | | | | | | | | | |
| Reporting of SAEs** | | | | | | | | | | | | |
| Reporting of fatal SAEs or SAEs related to study participation or GSK concomitant products | | | | | | | | | | | | |

* i.e. consent obtained; Pre-vacc.: pre-vaccination; Vacc.: vaccination; Post-vacc.: post-vaccination; D: Day; M: Month V: Vaccination.

** during the entire study period ending one month (minimum 31 days) following the last vaccination

† Reporting of solicited general AEs for liquid HRV vaccine will be done by all subjects excluding subjects in immunogenicity sub-cohort 2. Reporting of solicited general AEs for OPV vaccine and solicited general and local AEs for DTPa vaccine will be done only by subjects in immunogenicity subs-cohort 2.

[β] ***i.e. end of RV season in China.*** **Amended: 05 August 2011**

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 15. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

## 8.3.2. Evaluation of adverse events and serious adverse events

### 8.3.2.1. Active questioning to detect adverse events and serious adverse events

As a consistent method of soliciting AEs, the subject's parents/LARs should be asked a non-leading question such as:

'*Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?*'

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF or SAE Report screens as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to 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.

### 8.3.2.2. Assessment of adverse events

#### *8.3.2.2.1. Assessment of intensity*

Intensity of the following AEs will be assessed as described in Table 16:

**Table 16 Intensity scales for solicited symptoms reported during the solicited follow-up period**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Fever* | | Record temperature in °C |
| Irritability/Fussiness | 0 | Behaviour as usual |
| | 1 | Mild: Crying more than usual/no effect on normal activity |
| | 2 | Moderate: Crying more than usual/interferes with normal activity |
| | 3 | Severe: Crying that cannot be comforted/prevents normal activity |
| Diarrhoea¶ | | Record the number of looser than normal stools /day |
| Vomiting§ | | Record the number of vomiting episodes/day |
| Loss of appetite | 0 | Appetite as usual |
| | 1 | Mild: Eating less than usual/no effect on normal activity |
| | 2 | Moderate: Eating less than usual/interferes with normal activity |
| | 3 | Severe: Not eating at all |
| Cough/runny nose | 0 | Normal |
| | 1 | Mild: Cough/runny nose which is easily tolerated |
| | 2 | Moderate: Cough/runny nose which interferes with daily activity |
| | 3 | Severe: Cough/runny nose which prevents daily activity |
| Drowsiness | 0 | Behaviour as usual |
| | 1 | Mild: Drowsiness easily tolerated |
| | 2 | Moderate: Drowsiness that interferes with normal activity |
| | 3 | Severe: Drowsiness that prevents normal activity |
| Gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain) | 0 | Gastrointestinal symptoms normal |
| | 1 | Mild: Gastrointestinal symptoms that are easily tolerated |
| | 2 | Moderate: Gastrointestinal symptoms that interfere with normal activity |
| | 3 | Severe: Gastrointestinal symptoms that prevent normal activity |

*Fever is defined as temperature ≥ 37.1°C on axillary setting as defined by the Chinese authorities
¶Diarrhoea is defined as passage of three or more looser than normal stools within a day.
§Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day

**Table 17 Intensity scales used for diarrhoea, vomiting and fever reported during the solicited follow-up period**

| Adverse Experience | Intensity grade | Parameter |
|---|---|---|
| Diarrhoea | 0 | Normal (0 - 2 looser than normal stools/day) |
| | 1 | 3 looser than normal stools/day |
| | 2 | 4 - 5 looser than normal stools/day |
| | 3 | ≥ 6 looser than normal stools/day |
| Vomiting | 0 | Normal (no emesis) |
| | 1 | 1 episode of vomiting/day |
| | 2 | 2 episodes of vomiting/day |
| | 3 | ≥ 3 episodes of vomiting/day |
| Fever* | 0 | Axillary temperature < 37.1 °C |
| | 1 | Axillary temperature 37.1 °C - 37.5 °C |
| | 2 | Axillary temperature 37.6 °C - 39.0 °C |
| | 3 | Axillary temperature > 39.0 °C |
| Fever** | 0 | Axillary temperature < 37.5°C |
| | 1 | Axillary temperature ≥ 37.5 – ≤ 38.0°C |
| | 2 | Axillary temperature > 38.0 – ≤ 39.0°C |
| | 3 | Axillary temperature > 39.0°C |

*The maximum intensity of fever using the grading scale as defined by Chinese authorities.
**The maximum intensity of fever using the grading scale as defined by GSK Biologicals.

Intensity of the following solicited local AEs will be assessed as described in Table 18.

**Table 18 Intensity scales for solicited local symptoms**

| Adverse Event | Intensity grade | Parameter |
|---|---|---|
| Pain at injection site | 0 | None |
| | 1 | Mild: Minor reaction to touch |
| | 2 | Moderate: Cries/protests on touch |
| | 3 | Severe: Cries when limb is moved/spontaneously painful |
| Redness at injection site | | Record greatest surface diameter in mm |
| Swelling at injection site | | Record greatest surface diameter in mm |

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals using the guidelines of grading standards for AEs set by the Chinese authorities as follows:

| | | |
|---|---|---|
| 0 | : | Absent |
| 1 | : | < 15 mm |
| 2 | : | ≥ 15 mm and ≤ 30 mm |
| 3 | : | > 30 mm |

The investigator will assess the maximum intensity that occurred over the duration of the event for all other AEs, i.e. unsolicited symptoms, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

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

| | | |
|---|---|---|
| 1 (mild) | = | An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. |
| 2 (moderate) | = | An AE which is sufficiently discomforting to interfere with normal everyday activities. |
| 3 (severe) | = | An AE which prevents normal, everyday activities (in a young child, such an AE would, for example, prevent attendance at a day-care centre and would cause the parents/LARs to seek medical advice) |

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

#### *8.3.2.2.2. 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 plausible causes, based on 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 in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

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

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*Is there a reasonable possibility that the AE may have been caused by the liquid HRV vaccine?*

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

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined 'serious' (see Section 8.1.2 for definition of SAE), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

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

#### 8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e. unsolicited AE) or any SAE reported during the entire study will be assessed as:

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

#### 8.3.2.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject's parents/LARs will be asked if the subject received medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in eCRF.

## 8.4. Reporting and follow-up of adverse events, serious adverse events and pregnancies

### 8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs will be reported promptly to GSK as described in Table 19 once the investigator determines that the event meets the protocol definition of an SAE.

**Table 19 Time frames for submitting SAEs and other events reports to GSK Biologicals**

| Type of Event | Initial Reports | | Follow-up of Relevant Information on a Previous Report | |
|---|---|---|---|---|
| | Time Frame | Documents | Time Frame | Documents |
| All SAEs | 24 hours* | SAE screen | 24 hours* | SAE report/SAE screen |

* Time frame allowed after receipt or awareness of the information.

In case the electronic reporting system is temporarily unavailable, a backup system is in place. Please refer to Section 8.4.3 for a detailed description

**Study Contact for Reporting SAEs**

Please see the Sponsor Information Sheet for contact details.

**Back-up Study Contact for Reporting SAEs**

GSK Biologicals Clinical Safety and Pharamcovigilance

Fax: [redacted] or [redacted]

24/24 hour and 7/7 day availability

### 8.4.2. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1 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.

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 SAEs that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

### 8.4.3. Completion and transmission of SAEs reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional relevant information is received WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

#### 8.4.3.1. Back-up system in case the electronic SAE reporting system does not work

If the SAE reporting system has been down for 24 hours, the investigator or his/her delegate should fax an SAE report form directly to the GSK Central Safety department (please refer to Section 8.4.1) within 24 hours. The maximum timeline for reporting SAEs to central safety is therefore 48 hours.

NB. This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow.

As soon as the electronic reporting system is working again, the investigator or delegate must update the SAE screens in the eCRF within 24 hours.

The final valid information for regulatory reporting will be the information reported through the electronic system.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be sent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information.

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

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

### 8.4.4. Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

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, or until the event is otherwise explained, or the subject is lost to follow-up.

- Or, in the case of other non-serious AEs, until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the Site Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of additional clinical examinations/tests 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.

## 8.5. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.7.

## 8.6. Unblinding

GSK Biologicals' policy (incorporating ICH E2A 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 GSK Biologicals' Central Safety physician is responsible for

unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (refer to Section 8.4.1).

## 8.7. Emergency unblinding

The investigator, or other physician managing the subject, should contact GSK Biologicals' Central Safety Physician to discuss the need for emergency unblinding. Alternatively the investigator may contact the local contact who will contact the GSK Central Safety Physician.

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

An investigator should request for unblinding of the subject's treatment code only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study vaccines/product(s) is essential for the clinical management or welfare of the subject.

The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine(s)/product(s).

| **GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)** |
|---|
| Phones for 7/7 day availability:<br><br>Outside US/Canada:<br>[redacted] (GSK Biologicals Central Safety Physician)<br><br>Back-up mobile phone contact (all countries):<br>[redacted] |

## 8.8. Subject card

Subjects' parents/LARs must be provided with the address and telephone number of the main contact for information about the trial.

Investigator/delegate should therefore provide a "subject card" to each subject's parents/LARs. The aim of this card is to inform any physician having to deal with a subject in an emergency situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information.

Subjects' parents/LARs must be instructed to keep these cards in their possession at all times.

## 8.9. Assessment of GE episodes

Any GE episode (defined as diarrhoea with or without vomiting) occurring starting from Visit 1 to study end should be documented using the GE diary card. The following information will be collected on the GE diary card during each GE episode: Axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject and treatment given. The information collected on the GE diary card will allow the assessment of the intensity of each GE episode using a 20-point scoring system [Ruuska, 1990].

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

In the 20-point scoring system, points will be assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy (with use of oral rehydration fluids considered as marker for 1-5 % dehydration and use of intravenous fluids as marker for ≥ 6% dehydration) or hospitalisation (hospitalised subjects will be considered to have ≥ 6% dehydration) for each episode of GE as shown in Table 20.

**Table 20 The 20-point scoring system to determine the intensity of GE episodes reported during the study**

| Adverse Experience | Points |
|---|---|
| Duration of looser than normal stools (days) | |
| 1-4 | 1 |
| 5 | 2 |
| ≥ 6 | 3 |
| Maximum number of looser than normal stools /24 hours | |
| 1-3 | 1 |
| 4-5 | 2 |
| ≥ 6 | 3 |
| Duration of vomiting (days) | |
| 1 | 1 |
| 2 | 2 |
| ≥ 3 | 3 |
| Maximum number of episodes of vomiting/24 hours | |
| 1 | 1 |
| 2-4 | 2 |
| ≥ 5 | 3 |
| Fever∗<br>Axillary | |
| 36.6 – 37.9°C | 1 |
| 38.0 – 38.4°C | 2 |
| ≥ 38.5°C | 3 |
| Dehydration | |
| 1-5% | 2 |
| ≥ 6% | 3 |
| Treatment | |
| Rehydration | 1 |
| Hospitalisation | 2 |

∗The highest temperature recorded during the episode will be scored.

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

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

# 9. SUBJECT COMPLETION AND WITHDRAWAL

## 9.1. Subject completion

A subject who returns for the concluding visit in the protocol is considered to have completed the study.

## 9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/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 8.4).

Withdrawals will not be replaced.

### 9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered 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 in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject's parents/ LARs, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

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

### 9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to 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 vaccine 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 vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject's parents/ LARs or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-SAE.
- Other (specify).

# 10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

## 10.1. Primary endpoint

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period (two weeks post-Dose 2 till Visit 7).

## 10.2. Secondary endpoints

*Efficacy*

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***).
- Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till ***Visit 7***). **Amended: 05 August 2011**

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*Immunogenicity*

*(Immunogenicity Sub-cohort 1: To assess the immunogenicity of liquid HRV vaccine: N = 600 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as geometric mean concentration (GMC) at Visit 3 and at Visit 6.

*(Immunogenicity Sub-cohort 2: To assess the immunogenicity of the liquid HRV vaccine and co-administered childhood vaccines: N = 300 subjects)*

- Anti-rotavirus IgA antibody concentrations.
  - Anti-rotavirus IgA antibody seroconversion rate at Visit 3 and seropositivity rate at Visit 6.
  - Serum anti-rotavirus IgA antibody concentrations expressed as GMC at Visit 3 and at Visit 6.
- Immunogenicity against all antigens contained in each co-administered childhood vaccine:
  - Anti-tetanus, anti-diphtheria, anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), anti-pertactin (PRN), anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3 antibody concentrations/titres and seroprotection/seropositivity rates at Visit 5.

*Reactogenicity and Safety*

*All subjects except subjects in the immunogenicity sub-cohort 2:*

- Solicited general AEs of the liquid HRV vaccine
  - Occurrence of each general solicited symptom (fever, fussiness/irritability, loss of appetite, cough/runny nose, diarrhoea and vomiting) within the 8-day (Day 0 – Day 7) follow-up period after each dose of liquid HRV vaccine/placebo.

*Subjects in the immunogenicity sub-cohort 2:*

- Solicited local and general AEs of the co-administered childhood vaccines
  - Occurrence of local (pain, swelling, redness) and general solicited symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) within the 8-day (Day 0 – Day 7) follow-up period after the Dose 1 and Dose 2 of OPV vaccine and after Dose 1 of DTPa.

*All subjects:*

- Unsolicited AEs
  - Occurrence of unsolicited symptoms within the 31-day (Day 0 – Day 30) follow-up period after any dose of liquid HRV vaccine or placebo, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- SAEs
  - Occurrence of SAEs throughout the study period (after first vaccine dose till study end), according to the MedDRA classification.

## 10.3. Estimated sample size

Target enrolment will be 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated rate ***of non evaluable subjects*** is 20%.

Considering 1:1 randomisation ratio and various incidence rates, Table 21 provides the power to observe a lower limit of the 95% CI for vaccine efficacy to be above 0% and 10%.

For a 2% attack rate of RV GE in the placebo group from 2 weeks post Dose 2 to ***end of efficacy follow-up period***, and if the vaccine efficacy is 80%, the study has 95.8% power to observe a 95% CI for the vaccine efficacy that would be above 10%. It is expected to observe a total of 40 ***severe*** RV GE cases during the efficacy follow-up period in the total vaccinated cohort. **Amended: 05 August 2011**

**Table 21 Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 2600 evaluable subjects – 1300 subjects in HRV group and 1300 subject in the placebo group, power based on 1,000 simulations using Proc StatXact) Amended: 05 August 2011**

| Incidence rate in the Placebo for severe RV GE | VE (%) | Power to have a lower limit of the 95%CI on VE ≥ 0% | Power to have a lower limit of the 95%CI on VE ≥ 10% |
|---|---|---|---|
| ***1%*** | ***70*** | ***54.5%*** | ***44.2%*** |
| | ***80*** | ***69.6%*** | ***60.8%*** |
| 1.5% | 70 | 74.4% | 65.1% |
| | 80 | 87.8% | 82.7% |
| 2%* | 70 | 85.1% | 77.2% |
| | 80** | 97.6% | 95.8% |
| 2.5% | 70 | 92.7% | 87.8% |
| | 80 | 99.4% | 98.6% |
| 3% | 70 | 96.4% | 92.3% |
| | 80 | 99.4% | 99.3% |

*anticipated rate in the Placebo for severe RV GE.
VE - Vaccine Efficacy. CI-Confidence Interval
**anticipated vaccine efficacy
Attack Rate (AR) = 1.5% [1.0%; 2.3%], VE = 95.3% [73.1%;99.9%].

## 10.4. Study cohorts to be evaluated

### 10.4.1. Total vaccinated cohort

The total vaccinated cohort will include all subjects with at least one dose of the liquid HRV vaccine or placebo administration documented:

- A safety analysis based on the total vaccinated cohort will include all vaccinated subjects,
- An immunogenicity analysis based on the total vaccinated cohort will include all vaccinated subjects from the immunogenicity sub-cohorts for whom immunogenicity data are available,
- An efficacy analysis based on the total vaccinated cohort will include all vaccinated subjects for whom efficacy follow-up data are available.

### 10.4.2. According-To-Protocol cohort for analysis of safety

The ATP cohort for safety will include all vaccinated subjects:

- who have received at least one dose of HRV vaccine/Placebo according to their random assignment.
- for whom the randomisation code has not been broken, who have not received a vaccine forbidden by or not specified in the protocol.

### 10.4.3. According-to-protocol cohort for analysis of efficacy

The ATP cohort for efficacy will include all subjects from ATP cohort for safety.

- 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 received 2 doses of the liquid HRV vaccine or placebo,
- who have entered the efficacy surveillance period:
  - have follow-up beyond 2 weeks post Dose 2 of study vaccination
  - who have no RV other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks post Dose 2 of liquid HRV vaccine or placebo.

### 10.4.4. According-to-protocol cohort for analysis of immunogenicity

The ATP cohort for immunogenicity will include subjects in the immunogenicity sub-cohorts 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 the protocol defined age interval),
- who comply with vaccination schedule of liquid HRV vaccine or placebo,
- who comply with blood sampling schedule,
- for whom immunogenicity data was available, at pre and post sampling time-points,
- who have no concomitant infection unrelated to the vaccine which may influence the immune response,
- who have no RV other than vaccine strain in GE stool samples collected up to Visit 3,
- who were seronegative for serum anti-rotavirus IgA antibodies on the day of Dose 1.

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

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

## 10.5. Derived and transformed data

**Demography**

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

**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.

***The subjects, who have completed Visit 6 and have not given their consent to participate in the extension follow-up, will be considered as dropouts from the study. The ATP cohort for the analysis of efficacy will include all the subjects who have satisfied the points mentioned in the section 10.4.3.*** **Amended: 05 August 2011**

**Immunogenicity**

The cut-off value is defined by the laboratory before the analysis and is described in section 5.7.3.

- 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. The following seropositivity thresholds are applicable:
  - Anti-PT and anti-FHA antibody concentrations Greater than or equal to ≥ 20 El.U/ml
  - Anti-PRN should be at least a 4-fold increase in antibody concentration for the ratio of post-vaccination to pre-vaccination
  - Anti rotavirus antibody IgA antibody concentration ≥ to 20 U/mL

- A seroprotected subject is a subject whose antibody concentration/titre is greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:

  – Anti-diphtheria antibody concentrations ≥ 0.1 IU/ml.

  – Anti-tetanus antibody concentrations ≥ 0.1 IU/ml.

  – Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8.

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

- The GMCs calculations are performed by taking the anti-log of the mean of the log concentrations 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 the immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

**Safety/Reactogenicity**

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

## 10.6. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

### 10.6.1. Sequence of analyses

Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ***study conclusion***, an annex report will present ***all*** data up to ***study conclusion***. ***Immunogenicity analysis will be done with the case triggered analysis only if the serological results are available at that point in time or it will be presented in the annex report.***
**Amended: 05 August 2011**

### 10.6.2. Statistical considerations for interim analyses

No interim analysis is planned for the study.

## 10.7. Statistical methods

### 10.7.1. 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 and overall. The racial and gender composition will be presented. The mean, range and standard deviation of age in weeks at each dose of HRV vaccine or placebo will be calculated per group and over all. The distribution of subjects enrolled among the study centres will be tabulated as a whole and per group. The percentages of subjects who received concomitant and intercurrent vaccinations will be tabulated by group.

### 10.7.2. Analysis of efficacy

The ATP cohort for efficacy will be used for the primary analysis of efficacy. An analysis of efficacy based on the total vaccinated cohort will also be performed.

Vaccine efficacy will be calculated, with their 95% CI against:

- severe RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to G1 type caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe RV GE due to each non-G1 type during the efficacy follow-up period.
- hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.
- any and severe all cause GE during the efficacy follow-up period.
- Vaccine efficacy will also be derived from a Cox regression model on the time to first event with censoring for subjects without an event as an additional supportive & exploratory analysis.
- ***Vaccine efficacy analysis will also be performed on the data collected from 2 weeks post dose 2 of HRV vaccine /placebo up to visit 6. This will be presented as an additional supportive analysis.*** **Amended: 05 August 2011**

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The same analysis will also be performed on Total Vaccinated Cohort from dose 1 to study end.

### 10.7.3. Analysis of immunogenicity

The primary analysis will be based on the ATP cohort for the analysis of immunogenicity. If the percent of enrolled subjects excluded from this ATP cohort is more than 5%, a second analysis based on the Total Vaccinated cohort will be performed to complement the ATP analysis.

**For subjects in the immunogenicity sub-cohort 1:**

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

- Seroconversion rates at Visit 3 and seropositivity rate at Visit 6 and their exact 95% CI will be calculated.
- GMCs at Visit 3 and Visit 6 and their 95% CI will be calculated.
- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 will be displayed using reverse cumulative curves (RCCs).
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the placebo group will be computed.

**For subjects in the immunogenicity sub-cohort 2:**

For each treatment group, at each time-point that anti-rotavirus IgA anti-PT, anti-FHA, anti-PRN and anti-poliovirus serotype 1, 2 and 3 is measured

- Seroconversion rates at Visit 3 and seropositivity rate at Visit 6 and their exact 95% CI will be calculated.
- GMCs at Visit 3 and Visit 6 and their 95% CI will be calculated.
- The distribution of anti-rotavirus IgA antibody concentrations at Visit 3 and Visit 6 will be displayed using reverse cumulative curves (RCCs).
- The asymptotic standardised 95% CI for difference in the percentage of subjects who seroconverted for anti-rotavirus IgA antibody concentrations at Visit 3 between the HRV vaccine and the placebo group will be computed.
- Seroprotection rates and their exact 95% CIs for antibodies against diphtheria and tetanus and poliovirus types 1, 2 and 3 one month post Dose 3 of DTPa will be calculated.
- Seropositivity rates and their exact 95% CIs for antibodies against PT, FHA, PRN and poliovirus types 1, 2 and 3 one month post Dose 3 of DTPa will be tabulated.

- GMT/GMCs and their 95% CIs for antibodies against the vaccine antigens PT, FHA, PRN and poliovirus types 1, 2 and 3 one month post Dose 3 of DTPa will be calculated.

### 10.7.4. Analysis of safety

Note: Intensity of fever will be assessed by considering the grading scales recommended by the Chinese authorities as well as GSK Biologicals. Analysis for each scale will be performed separately.

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.

**For all subjects except subjects in the immunogenicity sub-cohort 2:**

The overall incidence, with exact 95% CI, of any AEs (solicited or unsolicited) during the solicited follow-up period will be tabulated by group, for each dose, for overall doses and per subject. The same calculations will be performed for any grade 3 (solicited or unsolicited) symptoms and for any (solicited or unsolicited) symptom related to vaccination.

The incidence, with exact 95% CI, of each individual solicited general symptom, will be calculated by group, over the solicited follow-up period, after each dose, for overall doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 3 and for each individual solicited general symptom related to vaccination.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

**For subjects in the immunogenicity sub-cohort 2:**

- The percentage of subjects with at least one local AE (solicited and unsolicited) after Dose 1 of DTPa, with at least one general AE (solicited and unsolicited) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa and with any AE during the 8-day (Day 0 – Day 7) follow-up period after the vaccination will be tabulated with exact 95% CI. The same calculations will be performed for any grade 3 (solicited or unsolicited)

symptoms, grade 3 related symptoms and for any symptoms requiring medical attention.

- The percentage of subjects reporting each individual solicited local symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 of DTPa and solicited general symptom (any grade 3, grade 3 related, and medically attended visit) after Dose 1 and Dose 2 of OPV and Dose 1 of DTPa during the 8-day (Days 0–7) follow-up period with exact 95% CI will be tabulated.
- Occurrence of fever and related fever will be reported per 0.5°C cumulative temperature increments.

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

**For all subjects:**

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to MedDRA. Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day follow-up period after any dose with its exact 95% CI will be tabulated by group, and by preferred term. Similar tabulation will be done for unsolicited AEs rated as grade 3 and for unsolicited AEs with causal relationship to vaccination.

The percentage of subjects who received at least one concomitant medication during the 8-day (Day 0 - Day 7) solicited follow-up period will be tabulated by type of medication, with exact 95% CI. Similar tabulations will be done for subjects who receive concomitant medication during the study period.

SAEs reported during the study period (i.e. from first vaccine dose till study end) will be described in detail.

***There will be a retrospective follow-up on SAEs for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2 and this will documented in the eCRF.*** **Amended: 05 August 2011**

# 11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

## 11.1. Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

## 11.2. Monitoring by GSK Biologicals

Monitoring visits by a GSK Site Monitor 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).

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF entries will serve as the source document.

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any amendments, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

## 11.3. Archiving of data at study sites

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); 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, 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.

## 11.4. Audits

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

## 11.5. Posting of information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

## 11.6. Ownership, confidentiality and publication

### 11.6.1. 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.

### 11.6.2. 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: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) 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.

### 11.6.3. 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 twenty-one working days, or at least 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.

### 11.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development.

In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

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# Appendix A AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

| **GlaxoSmithKline Biologicals**<br>Clinical Research & Development<br>**Protocol Amendment 1** | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Amendment number:** | Amendment 1 |
| **Amendment date:** | 02 September 2010 |
| **Co-ordinating author:** | [redacted] Scientific Writer |
| **Rationale/background for changes:** The following changes have been made in the protocol | |
| **Amended text has been indicated in *bold italics* in the following sections:**<br>**Section 5.2.2.1: Randomisation of supplies**<br>The randomisation will be performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals.<br><br>To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and thus to reduce the overall study recruitment period, ***6%*** ~~an~~ over-randomisation of supplies will be prepared.<br><br>The vaccine doses will be distributed to the study centres while respecting the randomisation block size. | |
| **Section 5.2.3: Randomisation of subjects to assay sub-cohorts**<br><br>***Randomisation for all the sub-cohorts will be done in parallel.*** ~~Randomisation order for the immunogenicity sub-cohorts will be as follows, the 1st 600 subjects will be randomised into immunogenicity sub-cohort 1 and the final 300 subjects will be randomised into immunogenicity sub-cohort 2.~~ Blood samples will be collected from both the sub-cohorts of subjects:<br><br>• Immunogenicity Sub-cohort 1 (Immunogenicity of liquid HRV vaccine, N = 600).<br><br>• Immunogenicity Sub-cohort 2 (Immunogenicity of liquid HRV vaccine and co-administered vaccines, N = 300). | |

**Section 6.7.1: Medications/products that may lead to the elimination of a subject from ATP analyses**

- Administration of a vaccine not foreseen by the study protocol during the period starting from ***14***~~30~~ days before each dose of the liquid HRV vaccine/placebo and ending ***14***~~30~~ days after, with the exception of routine childhood vaccinations.

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Amendment 2

# GlaxoSmithKline Biologicals

Clinical Research & Development

## Protocol Amendment 2

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Amendment number:** | Amendment 2 |
| **Amendment date:** | 05 August 2011 |
| **Co-ordinating author:** | [redacted] Scientific Writers |

**Rationale/background for changes:**
Based on the preliminary review of GE episodes reported to date prior to unblinding and complete cleaning of the database, the rotavirus (RV) attack rate seems lower than what was anticipated in the protocol. In order to have the acceptable statistical power for the primary endpoint, the efficacy follow-up needs to be extended till April 2012 (i.e. end of RV season in China).

In addition:

- The names of the co-ordinating and contributing authors have been updated on the title page.
- A few minor corrections such as typos and inconsistencies have been corrected.

**Amended text has been indicated in *bold italics* in the following sections:**

| | |
|---|---|
| **Contributing authors** | [redacted] ***Clinical Immunology representative*** |

**List of Abbreviations**

| | |
|---|---|
| ***NIFDC*** | ***National Institute for Food and Drug Control*** |

**1.1: Background**
The liquid HRV vaccine is currently registered in ~~over 50 countries~~ ***at least 77 countries*** worldwide including Mexico, Brazil, Australia and the European Union.

**In the Synopsis and Section 1.2: Rationale for the study and study design**
The primary objective of this study is to evaluate the efficacy of the liquid HRV vaccine to prevent severe RV GE during the efficacy follow-up period. There will be an efficacy follow-up starting 2 weeks after the second dose of study vaccination till ~~the infants are one year of age~~ ***April 2012 (i.e. end of RV season in China)***.

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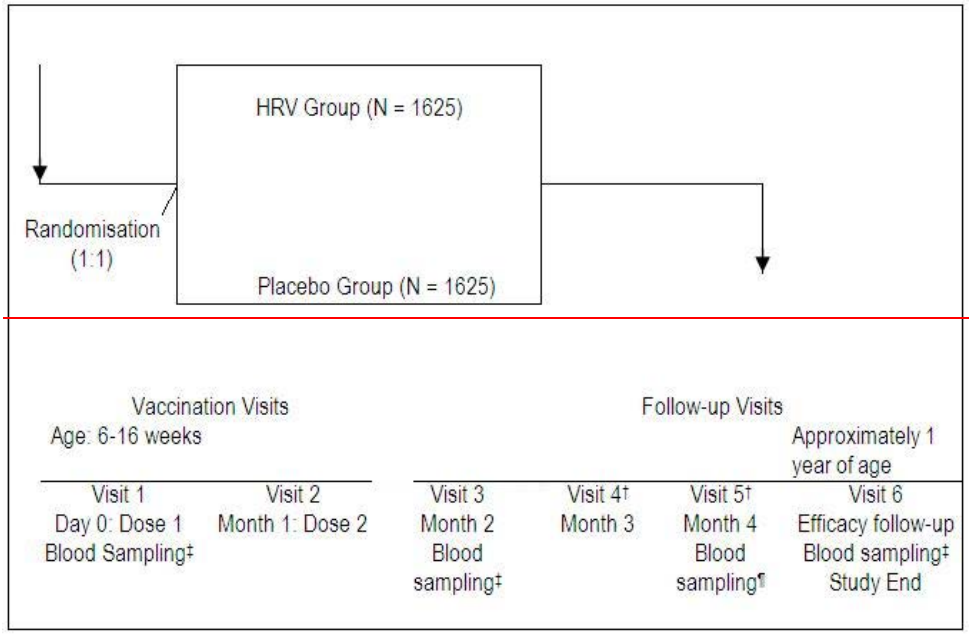
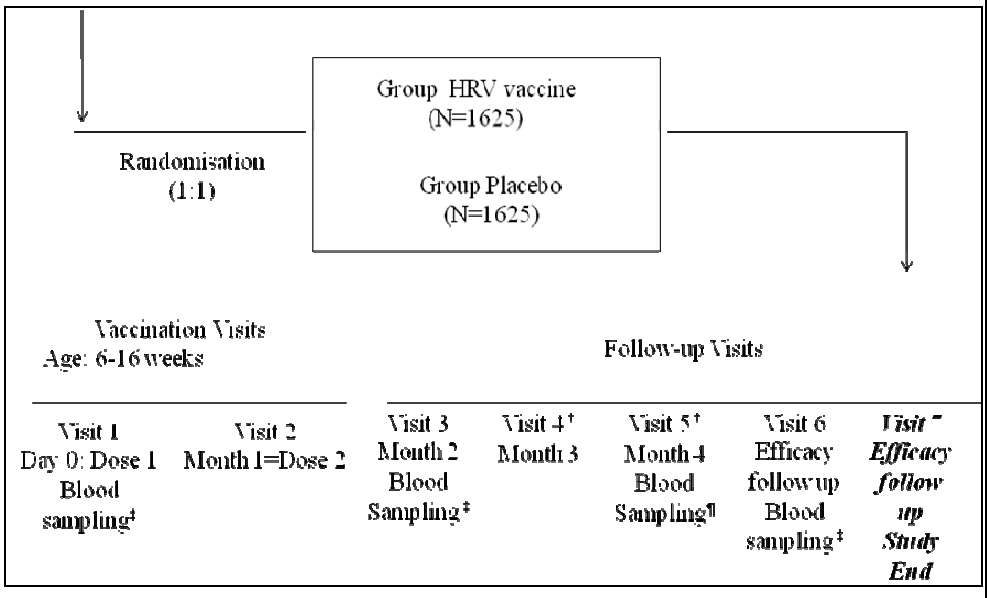
**In the Synopsis and Section 3: Study Design Overview**




N: Number of subjects planned to be enrolled
HRV: Human rotavirus
†Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort2.
‡Blood will be drawn from subjects in the immunogenicity sub-cohort 1 and immunogenicity sub-cohort 2.
¶ Blood will be drawn only from subjects in the immunogenicity sub-cohort 2.
Subjects in the immunogenicity sub-cohort 2 will receive a dose of OPV at Visit 1, Visit 2 and Visit 3; and will receive a dose of DTPa at Visit 2, Visit 3 and Visit 4

- Duration of the study: ***The subjects will be followed until April 2012 (i.e. end of RV season in China).*** The intended duration of the study, per subject, will ~~be till the subject is one year of age~~ ***not exceed a maximum of 21 months***. The study will have a single epoch as follows.
  - Primary: Primary starting Visit 1 (Day 0) and ending Visit ~~6~~***7*** ~~(1 year of age)~~ ***(April 2012 i.e. end of RV season in China)***.
- Recording of SAEs throughout the study period for all subjects.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up of SAEs will be done.***
- For each GE episode occurring during the study period,
  - a GE diary card should be completed daily until end of the GE symptoms.
  - a stool sample should be collected as soon as possible after GE symptoms begin.
  - ***for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2, a retrospective follow-up on GE-episodes will be done.***
- ***All parents/LARs of the subjects (including those subjects who have completed Visit 6 prior to the implementation of protocol amendment 2) will be contacted to ask if their children will participate in the extended follow-up (Visit 7).***
- ***The additional informed consent will be taken for the extended follow-up.***
- Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ~~when all subjects have reached one year of age~~ ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ~~all subjects reach one year of age~~ ***study conclusion***, an annex report will present ***all*** ~~the efficacy/safety~~ data up to ~~one year of age~~ ***study conclusion***.

**Section 4.1: Number of subjects/centres**

- The intended duration of the study, per subject, will ~~be till the subject is one year of age~~ ***not exceed a maximum of 21 months***.

**Section 5.5: Outline of study procedures**
**Table 5: List of study procedures**

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Amendment 2

| **Age** | **6 to 16 weeks** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Epoch** | **Primary** | | | | | **Efficacy follow-up** | |
| **Type of contact** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4 *** | **Visit 5 *** | **Visit 6** | ***Visit 7*** |
| **Time-points** | **Days 0** | **Months 1** | **Months 2** | **Months 3** | **Months 4** | ***Approximately* Years 1 of age** | ***April 2012[β]*** |
| **Sampling time-points** | **Pre-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Efficacy follow up** | ***Efficacy follow up*** |
| Informed consent | ● | | | | | | |
| ***Re-consenting for Visit 7 follow-up*** | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | O | O | O | O | O | O |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approximately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approximately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approximately 3mL: sub-cohort 2) | ● (Approxima-tely 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+DTPa) | ● (OPV+DTPa) | ● (DTPa) | | | |

| **Age** | **6 to 16 weeks** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Epoch** | **Primary** | | | | | **Efficacy follow-up** | |
| **Type of contact** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4 *** | **Visit 5 *** | **Visit 6** | ***Visit 7*** |
| **Time-points** | **Days 0** | **Months 1** | **Months 2** | **Months 3** | **Months 4** | ***Approximately* Years 1 of age** | ***April 2012[8]*** |
| **Sampling time-points** | **Pre-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Post-Vacc** | **Efficacy follow up** | ***Efficacy follow up*** |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of ~~non-SAEs~~ ***unsolicited AEs*** within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | O | O | O | O | O | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | ● | ● |
| Study Conclusion | | | | | | ● | ● |

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
*Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort 2.
**Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
***β i.e. end of RV season in China.***

**Table 6: Intervals between study visits**

| Interval | Optimal length of interval [1] | Maximum interval allowed [2] |
|---|---|---|
| 1 (Visit 1) →(Visit 2) | 30-48 days | 21-48 days |
| 2 ((Visit 2 →(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3 →(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | ~~by one year of age~~ ***1 year of age ± 2 weeks[γ]*** | ***1 year of age ± 30 days*** |
| ***6 (Visit 6) → (Visit 7)*** | ***01 April 2012 to 30 April 2012[γ]*** | ***01 April 2012 to 31 May 2012*** |

[1]. Whenever possible the investigator should arrange study visits within this interval
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they make the study visit outside this interval
Note: The date of the previous visit serves as the reference date for intervals between study visits. Refer to section 3 for details on the study visits applicable to the subjects in the study.
***[γ] It is a defined time point for follow up visit in a range and not an interval***

**Section 5.6.3.12: Recording GE occurring throughout the study period in a GE diary card**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.3.13: Collection of stool samples in case the child develops GE**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.3.14: Return of diary cards and GE diary cards**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.3.15: Diary card and GE diary card transcription by investigator**
This procedure is followed for all subjects on Visits 1, 2, 3, 6 ***and 7***.

**Section 5.6.4: Procedures during Efficacy follow-up *(Visit 6)***

***For subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2:***

***The additional consent will be obtained from the subject's parents/LARs. Retrospective data on intercurrent medical condition, concomitant medication/vaccination, GE episodes and SAEs will also be collected.***

***For subjects who are returning for Visit 6 after the implementation of protocol amendment 2:***
Note that some of the procedures to be performed during the follow-up visits (such as physical examination, blood sampling, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of ***S***AEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11. ***For the participation in the extended follow-up till Visit 7, additional consent of subject's parents/LARs will be obtained.***

***Section 5.6.5: Procedures during Efficacy follow-up (Visit 7)***
***Note that some of the procedures to be performed during the follow-up visits (such as physical examination, recording of GE, collection of stool samples, collection of GE and diary cards and its transcription, recording of concomitant medication and intercurrent medical condition and recording of SAEs) are also performed during the other visits of the primary epoch and are described in Section 5.6.3 up to Section 5.6.3.11.***

**Section 5.7.2: Biological samples**
**Table 7: Biological samples**

| Sample type | Quantity | Unit | Time-point | Sub-cohort Name* |
|---|---|---|---|---|
| Blood | Approximately 3 | ml | Schedule (Visit 1) Days 0 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 4 .5 | ml | Schedule (Visit 1) Days 0 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) Months 2 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 3) Months 2 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 5) Months 4 | Immunogenicity Sub-cohort 2 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) Years 1 | Immunogenicity Sub-cohort 1 |
| Blood | Approximately 3 | ml | Schedule (Visit 6) Years 1 | Immunogenicity Sub-cohort 2 |
| Stool | NA | NA | Schedule From Visit 1 (Days 0) to Visit ~~6 (1 year)~~ ***7 (April 2012)***$^{\beta}$ | All subjects |

Refer to Section 5.2.3 for sub-cohort description.
NA=Not applicable
$^{\beta}$ ***i.e end of RV season in China.***

**Section 5.7.2: Biological samples**
**Table 9: Immunological read-outs**

| Blood sampling time-point | | Sub-cohort Name | No.of subjects | Component | Components priority rank |
|---|---|---|---|---|---|
| Type of contact and time-point | Sampling time-point | | | | |
| Visit 1 (Days 0) | Pre-Vacc | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 1 (Days 0) | Pre-Vacc | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | IgA anti-HRV, Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 3 (Months 2) | Post-Vacc § | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 3 (Months 2) | Post-Vacc § | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| Visit 5 (Months 4) | Post-Vacc * | Immunogenicity Sub-cohort 2 | 300 | Poliovirus serotypes 1, 2 and 3, D, T, PT, FHA, PRN | Poliovirus serotypes 1, 2 and 3, D,T, PT, FHA, PRN |
| Visit 6 (Years 1) | Efficacy follow up | Immunogenicity Sub-cohort 1 | 600 | IgA anti-HRV | None |
| Visit 6 (Years 1) | Efficacy follow up | Immunogenicity Sub-cohort 2 | 300 | IgA anti-HRV | None |
| **GE stool analysis** | | | | | |
| Visit 1 (Days 0) to Visit ~~6 (At 1 year of age)~~ ***7 (April 2012)$^{\beta}$*** | Throughout the study period | All subjects | | RV antigen | None |

D = Diphtheria, T = Tetanus
§ Post-Vacc 2: One month post Dose 2 of liquid HRV vaccine/placebo
*Post-Vacc 3: Two month post Dose 3 of OPV and one month post of Dose 3 of DTPa
***$^{\beta}$ i.e. end of RV season in China.***

**Section 5.7.3: Laboratory assays**
**Table 8: Laboratory assays**

| System | Component | Method | Test Kit / Manufacturer | Unit | Cut-off | Laboratory |
|---|---|---|---|---|---|---|
| Serum | anti-rotavirus | IgA ELISA | In-house | U/mL | 20 | GSK Biologicals* |
| Serum | anti-diphtheria | ELISA** | ~~NICPBP~~ ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-tetanus | ELISA** | ~~NICPBP~~ ***NIFDC*** | IU/mL | 0.1 | GSK Biologicals* |
| Serum | anti-PT | ELISA** | ~~NICPBP~~ ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-FHA | ELISA** | ~~NICPBP~~ ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-PRN | ELISA** | ~~NICPBP~~ ***NIFDC*** | EL.U/mL | 5 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 1 | Micro-neutralisation test | ~~NICPBP~~ ***NIFDC*** | ED50† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 2 | Micro-neutralisation test | ~~NICPBP~~ ***NIFDC*** | ED50† | 1:8 | GSK Biologicals* |
| Serum | anti-poliovirus serotype 3 | Micro-neutralisation test | ~~NICPBP~~ ***NIFDC*** | ED50† | 1:8 | GSK Biologicals* |

GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals in China.
**or Multiplex
ELISA = Enzyme Linked Immunosorbent Assay
~~NICPBP~~ ***NIFDC*** = National Institute for ~~the control of Pharmaceutical and Biological~~ ~~Product~~ ***Food and Drug Control***
U = Units; IU = International Units; EL.U = Elisa Units
†ED50 = Estimated dose 50% is the seroprotective level.

**Section 6.7.2: Time window for recording concomitant medication/vaccination in the eCRF**

***All medications given for the protocol defined GE episode that occur during the period starting with the administration of each dose of study vaccine and ending 31 days after each dose of study vaccine must be recorded both in the concomitant medication section of the eCRF and in the respective GE section of the eCRF. The medications given for the protocol defined GE episode occurring outside the window of 31 days post vaccination must be recorded only in the respective GE section of the eCRF.***

**Section 8.3.1:Time period for detecting and recording adverse events, serious adverse events**
**Table 15: Reporting periods for adverse events, serious adverse events**

| Study activity | Pre Vacc* | V1 Dose 1 | 7 days post-vacc | 30 days post-vacc | V2 Dose 2 | 7 days post-vacc | 30 days post-vacc | V3 | V4 | V5 | V6 | *Study Conclusion V7* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | D0 | | | M1 | | | M2 | M3 | M4 | *Approximately* One year of age | *April 2012[β]* |
| Reporting of solicited local and/or general AEs† | | | | | | | | | | | | |
| Reporting of unsolicited AEs | | | | | | | | | | | | |
| Reporting of SAEs** | | | | | | | | | | | | |
| Reporting of fatal SAEs or SAEs related to study participation or GSK concomitant products | | | | | | | | | | | | |

* i.e. consent obtained; Pre-vacc.: pre-vaccination; Vacc.: vaccination; Post-vacc.: post-vaccination; D: Day; M: Month V: Vaccination.
** during the entire study period ending one month (minimum 31 days) following the last vaccination
† Reporting of solicited general AEs for liquid HRV vaccine will be done by all subjects excluding subjects in immunogenicity sub-cohort 2. Reporting of solicited general AEs for OPV vaccine and solicited general and local AEs for DTPa vaccine will be done only by subjects in immunogenicity subs-cohort 2.
***[β] i.e. end of RV season in China.***

**In the Synopsis and Section 10.1: Primary endpoint**

- Occurrence of severe RV GE caused by the circulating wild-type RV strains in subjects vaccinated with liquid HRV vaccine/placebo during the efficacy follow-up period ***(two weeks post-Dose 2 till Visit 7)***.

**In the Synopsis and Section 10.2: Secondary endpoints**

- Occurrence of RV GE in subjects vaccinated with liquid HRV vaccine/placebo.
  - Occurrence of any RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).
  - Occurrence of any and severe RV GE caused by the RV strains of each non-G1 type during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).
  - Occurrence of hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).

Occurrence of any and severe all cause GE during the efficacy follow-up period (two weeks post-Dose 2 till ~~the subjects reach one year of age~~ ***Visit 7***).

**Section 10.3: Estimated sample size**

Target enrolment will be 3250 subjects (1625 subjects in each group) to obtain 2600 evaluable subjects (1300 subjects in each group) for the evaluation of the primary objective. The estimated ~~dropout~~ rate ***of non evaluable subjects*** is 20%.

For a 2% attack rate of RV GE in the placebo group from 2 weeks post Dose 2 ~~up~~ to ~~one year of age~~ ***end of efficacy follow-up period***, and if the vaccine efficacy is 80%, the study has 95.8% power to observe a 95% CI for the vaccine efficacy that would be above 10%. It is expected to observe a total of 40 ***severe*** RV GE cases during the efficacy follow-up period in the total vaccinated cohort.

**Table 21 : Power to observe a lower limit of the 95%CI for Vaccine Efficacy (VE) above 0% and 10% for various incidence rates and true VE (N = 2600 evaluable subjects – 1300 subjects in HRV group and 1300 subject in the placebo group, power based on 1,000 simulations using Proc StatXact)**

| Incidence rate in the Placebo for severe RV GE | VE (%) | Power to have a lower limit of the 95%CI on VE ≥ 0% | Power to have a lower limit of the 95%CI on VE ≥ 10% |
|---|---|---|---|
| ***1%*** | ***70*** | ***54.5%*** | ***44.2%*** |
| | ***80*** | ***69.6%*** | ***60.8%*** |
| 1.5% | 70 | 74.4% | 65.1% |
| | 80 | 87.8% | 82.7% |
| 2%* | 70 | 85.1% | 77.2% |
| | 80** | 97.6% | 95.8% |
| 2.5% | 70 | 92.7% | 87.8% |
| | 80 | 99.4% | 98.6% |
| 3% | 70 | 96.4% | 92.3% |
| | 80 | 99.4% | 99.3% |

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|---|
| *anticipated rate in the Placebo for severe RV GE.<br>VE - Vaccine Efficacy. CI-Confidence Interval<br>**anticipated vaccine efficacy<br>Attack Rate (AR) = 1.5% [1.0%; 2.3%], VE = 95.3% [73.1%;99.9%]. |
| **Section 10.5: Derived and transformed data**<br>**Effiacy**<br>***The subjects, who have completed Visit 6 and have not given their consent to participate in the extension follow-up, will be considered as dropouts from the study. The ATP cohort for the analysis of efficacy will include all the subjects who have satisfied the points mentioned in the section 10.4.3.*** |
| **Section 10.6.1: Sequence of analyses**<br>Final analysis will be done when 40 severe RV GE episodes caused by the circulating wild-type RV strains is reached during the efficacy follow-up period or ~~when all subjects have reached one year of age~~ ***at study conclusion***, whichever is the earliest. If the number of cases of required severe RV GE caused by the circulating wild-type RV strains is reached before ~~all subjects reach one year of age~~ ***study conclusion***, an annex report will present ~~the efficacy/safety~~ ***all*** data up to ~~one year of age~~ ***study conclusion***.<br>***Immunogenicity analysis will be done with the case triggered analysis only if the serological results are available at that point in time or it will be presented in the annex report.*** |
| **Section 10.7.2 Analysis of efficacy**<br>***Vaccine efficacy analysis will also be performed on the data collected from 2 weeks post dose 2 of HRV vaccine/placebo up to visit 6. This will be presented as an additional supportive analysis.*** |
| **Section 10.7.4 Analysis of safety**<br>***There will be a retrospective follow-up on SAEs for subjects who have already completed Visit 6 prior to the implementation of protocol amendment 2and this will document in the eCRF.*** |

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113808 (ROTA-075)
Final

## Protocol Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 . |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted] Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | [redacted] |
| **Date** | 7 July 2010 |

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## Protocol Investigator Agreement

**I agree:**

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (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.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- 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 documents required by regulatory agencies for this study.

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113808 (ROTA-075)
Final

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | [redacted] |
| **Signature** | [redacted] |
| **Date** | 20/ jun / 2010 |

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# Protocol Amendment 1 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 |
| **Date of protocol amendment** | Amendment 1: 2 Sep 2010 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted] Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | [redacted] |
| **Date** | 10 Sep 2010 |

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113808 (ROTA-075)
Amendment 1

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 Jun 2010 |
| **Date of protocol amendment** | Amendment 1: 2 Sep 2010 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | [redacted] |
| **Signature** | |
| **Date** | 03 - Nov-2010 |

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## Protocol Amendment 2 Sponsor Signatory Approval

| | |
|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010. |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Sponsor signatory** | [redacted]<br>Director, Rotavirus vaccines, Global Clinical Research and Development Centre, USA. |
| **Signature** | [redacted] |
| **Date** | Aug 22, 2011 |

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|---|---|
| **eTrack study number and Abbreviated Title** | 113808 (ROTA-075) |
| **IND number** | 2009L10238 |
| **Date of protocol** | Final: 10 June 2010 |
| **Date of protocol amendment 1** | Amendment 1 Final: 02 September 2010 |
| **Date of protocol amendment 2** | Amendment 2 Final: 05 August 2011 |
| **Detailed Title** | A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants. |
| **Investigator name** | [redacted] |
| **Signature** | |
| **Date** | 03-08-2011 |

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# Sample Case Report Form

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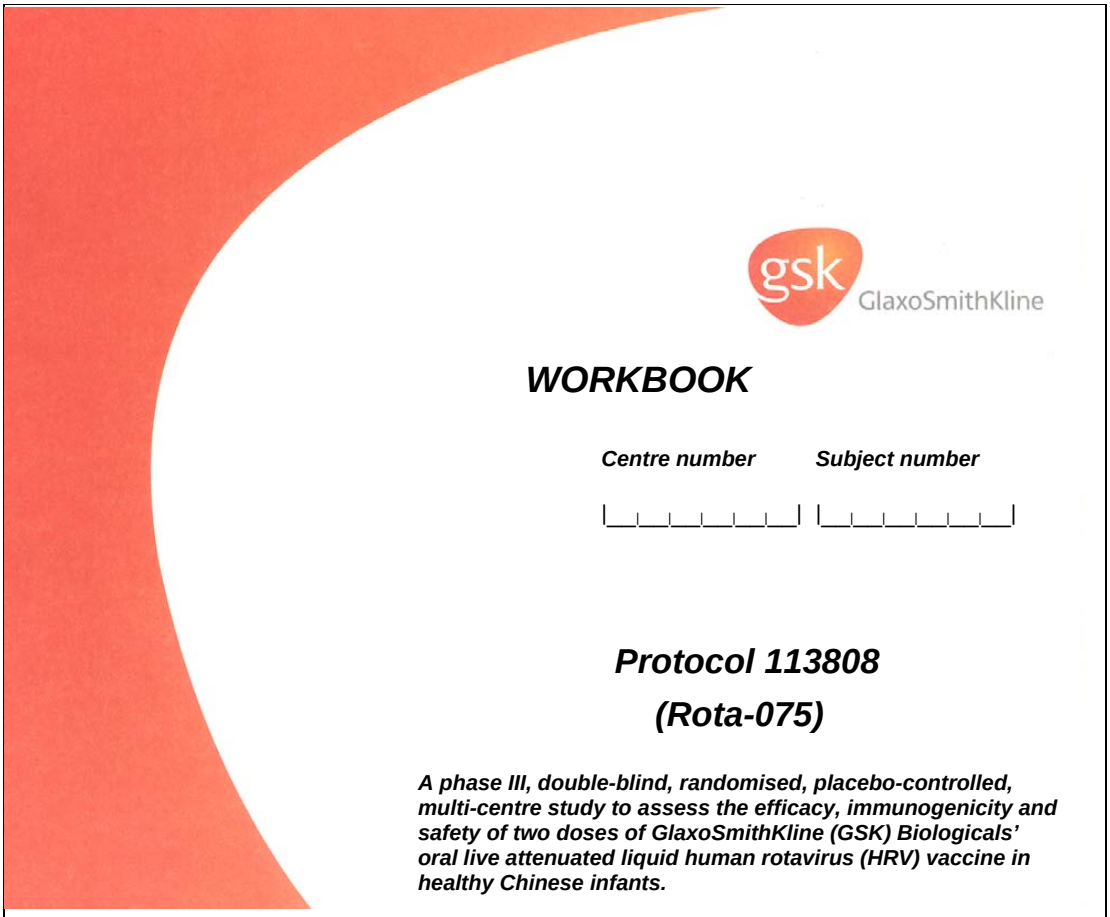

GlaxoSmithKline

# *WORKBOOK*

***Centre number*** ***Subject number***

|__|__|__|__|__|__| |__|__|__|__|__|__|

## *Protocol 113808*
## *(Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

GlaxoSmithKline Biologicals

Rue de l'Institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted]

## GENERAL INSTRUCTIONS

**ABBREVIATIONS**
Abbreviations for medical conditions, clinical events or drug names are to be avoided.

**DATES**
Use the following 3-letter abbreviations to indicate months:

| | | |
|---|---|---|
| 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 8**| = 1st January 2008

**MISSING DATA CODES**
Preferably use following codes:

ND = Not Done
NA = Not Applicable
NK = Not Known

For all subjects participating to an epoch (or to a study if only one epoch), the **End of epoch** (or the Study Conclusion if only one epoch) and the corresponding **Medication, Concomitant Vaccination, (S)AE sections** must be completed.

If a subject doesn't participate to an epoch (or to a study if only one epoch), neither the **End of epoch** (or the Study Conclusion if only one epoch) nor the corresponding **Medication, Concomitant Vaccination, (S)AE sections** have to be completed.

.

# ADVERSE EVENT DEFINITIONS

## INTENSITY FOR SOLICITED SYMPTOMS

**Solicited general adverse events for liquid HRV vaccine/placebo (excluding subjects in immunogenicity sub-cohort 2)**

***Fever :*** Record temperature in °C

***Irritability/Fussiness***
**0**: Behavior as usual
**1**: Mild: Crying more than usual / no effect on normal activity
**2**: Moderate: Crying more than usual / interferes with normal activity
3**:** Severe: Crying that cannot be comforted / prevents normal activity

***Loss of appetite***
**0**: Appetite as usual
**1**: Mild: Eating less than usual / no effect on normal activity
**2**: Moderate: Eating less than usual / interferes with normal activity
**3**: Severe: Not eating at all

***Cough/runny nose***
**0**: Normal
**1**: Mild: Cough/runny nose which is easily tolerated
**2**: Moderate: Cough/runny nose which interferes with daily activity
**3**: Severe: Cough/runny nose which prevents daily activity

***Diarrhea* :** Record the number of looser than normal stools /day

***Vomiting :*** Record the number of vomiting episodes/day

**Solicited adverse events for co-administered childhood vaccines**

***Pain***
**0**: None
**1**: Mild: Minor reaction to touch
**2**: Moderate: Cries/protests on touch
3**:** Severe: Cries when limb is moved/spontaneously painful

***Irritability/Fussiness***
**0**: Behavior as usual
**1**: Mild: Crying more than usual / no effect on normal activity
**2**: Moderate: Crying more than usual / interferes with normal activity
3**:** Severe: Crying that cannot be comforted / prevents normal activity

***Loss of appetite***
**0**: Appetite as usual
**1**: Mild: Eating less than usual / no effect on normal activity
**2**: Moderate: Eating less than usual / interferes with normal activity
**3**: Severe: Not eating at all

Redness at injection site: Record greatest surface diameter in mm

Swelling at injection site: Record greatest surface diameter in mm

***Drowsiness***
**0**: Behaviour as usual
**1**: Mild: Drowsiness easily tolerated
**2**: Moderate: Drowsiness that interferes with normal activity
**3:** Severe:Drowsiness that prevents normal activity

**Gastrointestinal symptoms (**nausea, vomiting, diarrhea and/or abdominal pain)

**0**: Gastrointestinal symptoms normal
**1**: Mild: Gastrointestinal symptoms that are easily tolerated
**2**: Moderate: Gastrointestinal symptoms that interfere with normal activity
**3:** Severe:Gastrointestinal symptoms that prevent normal activity

***Fever*** *:* Record temperature in °C

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# ADVERSE EVENT DEFINITIONS

## INTENSITY FOR UNSOLICITED SYMPTOMS

**1: Mild:** An adverse event (AE) which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
**2: Moderate:** An AE which is sufficiently discomforting to interfere with normal everyday activities.
**3: Severe:** An AE which prevents normal, everyday activities
(In a young child, such an AE would, for example, prevent attendance at school/kindergarden/a day-care centre and would cause the parents/legally acceptable representatives 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: the 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: the 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: the AE is the cause of death (only applicable for serious adverse event reports)

## SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is any untoward medical occurrence that:
• results in death
• is life threatening
• results in persistent or significant disability / incapacity
• requires in-patient hospitalization
• requires prolongation of existing hospitalization
• is a congenital anomaly / birth defect in the offspring of a study subject
• In addition, important medical events that may not be immediately life-threatening or result in death or hospitalisation but that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above should also be considered serious. (Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
For each SAE the investigator becomes aware of, please complete and submit a **Serious Adverse Event (SAE)** report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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**113808 (Rota-075)**

# OUTLINE OF STUDY PROCEDURES

**List of study procedures**

| Age | 6 to 16 weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Epoch | Primary | | | | | Efficacy follow-up | |
| Type of contact | Visit 1 | Visit 2 | Visit 3 | Visit 4 * | Visit 5 * | Visit 6 | *Visit 7* |
| Time-points | Days 0 | Months 1 | Months 2 | Months 3 | Months 4 | *Years* 1 of age | *April 2012*[β] |
| Sampling time-points | Pre-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Post-Vacc | Efficacy follow up | *Efficacy follow up* |
| Informed consent | ● | | | | | | |
| *Re-consenting for Visit 7 follow-up* | | | | | | ● | |
| Check inclusion criteria | ● | | | | | | |
| Check exclusion criteria | ● | | | | | | |
| Check Contraindications | ● | ● | | | | | |
| Check warnings and precautions | ● | ● | | | | | |
| Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis. | ● | ● | ● | ● | | | |
| Medical history | ● | | | | | | |
| Physical examination | ● | O | O | O | O | O | O |
| Pre-vaccination body temperature | ● | ● | | | | | |
| Measure/record height and weight | ● | | | | | | |
| Recording of gestational age | ● | | | | | | |
| Randomisation | ● | | | | | | |
| Blood sampling for antibody determination | ● (Approxi-mately 3mL: sub-cohort 1 and 4.5 mL: sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 1 and sub-cohort 2) | | ● (Approxim-ately 3mL: sub-cohort 2) | ● (Approxima-tely 3mL: sub-cohort 1 and sub-cohort 2) | |
| Vaccination (HRV vaccine or placebo) | ● | ● | | | | | |
| Recording of co-administered vaccines in sub-cohort 2 | ● (OPV) | ● (OPV+DTPa) | ● (OPV+DTPa) | ● (DTPa) | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 –Day 7) after each dose of liquid HRV vaccine/placebo by subjects' parents/LARs | ● | ● | | | | | |
| Daily post-vaccination recording of solicited general AEs within 8-days (Day 0 – Day 7) after Dose 1 and Dose 2 of OPV by subjects' parents/LARs | ● ** | ● ** | | | | | |
| Daily post-vaccination recording of solicited local and general AEs within 8-days (Day 0 – Day 7) after Dose 1 of DTPa by subjects' parents/LARs | | ● ** | | | | | |
| Recording of *unsolicited AEs* within 31 days (Day 0 – Day 30) post-vaccination , by investigator | ● | ● | ● | | | | |
| Recording GE occurring throughout the study period in a GE diary card | ● | ● | ● | ● | ● | ● | ● |
| Collection of stool samples in case the child develops GE | ● | ● | ● | ● | ● | ● | ● |
| Return of diary cards and GE diary cards | | O | O | O | O | O | ● |
| Diary card and GE diary card transcription by investigator | | ● | ● | ● | ● | ● | ● |
| Record any concomitant medication/vaccination | ● | ● | ● | ● | ● | ● | ● |
| Record any intercurrent medical condition | ● | ● | ● | ● | ● | ● | ● |
| Recording of SAEs | ● | ● | ● | ● | ● | ● | ● |
| Analysis on clean data | | | | | | | ● |
| Study Conclusion | | | | | | | ● |

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**113808 (Rota-075)**

# OUTLINE OF STUDY PROCEDURES

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
LAR = Legally Acceptable Representative
* Visit 4 and Visit 5 will be applicable only to subjects in the immunogenicity sub-cohort 2.
** Study procedures applicable only to subjects in the immunogenicity sub-cohort 2
*[β] i.e. end of the RV season in China. Amended: 05 August 2011*

## Intervals between study visits

| Interval | Optimal length of interval [1] | Maximum interval allowed [2] |
|---|---|---|
| 1 (Visit 1)→(Visit 2) | 30-48 days | 21-48 days |
| 2 ((Visit 2)→(Visit 3) | 30-48 days | 21-48 days |
| 3 (Visit 3)→(Visit 4) | 30-48 days | 21-48 days |
| 4 (Visit 4) → (Visit 5) | 30-48 days | 21-48 days |
| 5 (Visit 5) → (Visit 6) | *1 year of age±2 weeks[γ]* | *1 year of age ±30 days* |
| *6 (Visit 6) → (Visit 7)* | *01 April 2012 to 30 April 2012[γ]* | *01 April 2012 to 31 May 2012* |

[1]. Whenever possible the investigator should arrange study visits within this interval
[2]. Subjects will not be eligible for inclusion in the According-To-Protocol (ATP) cohort for analysis if they make the study visit outside this interval
*[γ] It is a defined time point for follow up visit in a range and not an interval. Amended: 05 August 2011*
Note: The date of the previous visit serves as the reference date for intervals between study visits. Refer to section Error! Reference source not found. for details on the study visits applicable to the subjects in the study.

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**113808 (Rota-075)**

| | | | Centre Number | Subject Number |
|---|---|---|---|---|
| | | | \|__\|__\|__\|__\|__\|__\| | \|__\|__\|__\|__\|__\|__\| |

# DEMOGRAPHICS

**Date of Birth:** |__|__| |__|__|__| |__|__|__|__|
day month year

**Gender:**

[M] ☐ Male
[F] ☐ Female

**Geographic Ancestry:**

[91] ☐ Asian – Chinese Heritage
[99] ☐ Other, specify: _____

## SUBJECT SUB-COHORT

Please specify sub-cohort:

☐ Immunogenicity sub-cohort 1
☐ Immunogenicity sub-cohort 2
☐ Non Immunogenicity cohort

1

**VISIT 1**

**DAY 0**

# Informed Consent has to be obtained prior to any study procedure

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year | \|__\|__\|__\|__\|__\|__\|__\| |

# INFORMED CONSENT

*I certify that Informed Consent has been obtained prior to any study procedure.*

Informed Consent Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Did the subject agree that her/his biological samples(s) may be used by GSK Biologicals for further research that is NOT RELATED to the study vaccine(s)/product(s) or the disease(s) under study? [type 4 tests]

☐ Yes ☐ No ☐ NA

2

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **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 of the 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 parent(s)/Legally Acceptable Representative(s) (LAR) can and will comply with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).

[2] ☐ A male or female infant of Chinese origin between, and including, 6 and 16 weeks (42-112 days) of age at the time of the first vaccination.

[3] ☐ Written informed consent obtained from the parent(s)/LAR of the subject.

[4] ☐ Healthy subjects as established by medical history and clinical examination before entering into the study.

[5] ☐ Born after a gestation period of 36 to 42 weeks inclusive.

## EXCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[6] ☐ Child in care.

- Please refer to the GLOSSARY OF TERMS for the definition of child in care.

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

[8] ☐ Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth. For corticosteroids, prednisone 0.5 mg/kg/day, or equivalent, inhaled and topical steroids are allowed.

[9] ☐ Planned administration/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.of the first dose of the HRV vaccine or placebo except for the routine childhood vaccinations.

[10] ☐ 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).

[11] ☐ Any clinically significant history of gastrointestinal disease including any uncorrected congenital malformation (such as Meckel's diverticulum) of the gastrointestinal tract that would predispose for IS.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | | _____ |

# ELIGIBILITY CHECK – continued

## EXCLUSION CRITERIA

Tick (✓) the boxes corresponding to any of the exclusion criteria that disqualified the subject from entry.

[ 12 ] ☐ Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

[ 13 ] ☐ Family history of congenital or hereditary immunodeficiency.

[ 14 ] ☐ History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.

[ 15 ] ☐ Major congenital defects or serious chronic illness.

[ 16 ] ☐ History of confirmed RV GE.

[ 17 ] ☐ Acute disease and/or fever at the time of enrolment.

- Fever is defined as temperature (37.1°C on axillary setting as defined by the Chinese authorities.
- Subjects with a minor illness (such as mild diarrhea mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator (warrants deferral of the vaccination).

[ 18 ] ☐ GE within 7 days preceding the study vaccine or placebo administration (warrants deferral of the vaccination).

[ 19 ] ☐ Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

**In addition to the criteria mentioned above, the following criteria will be applicable to all subjects in the immunogenicity sub-cohort 2:**

[ 20 ] ☐ History of diphtheria, tetanus and pertussis disease.

[ 21 ] ☐ History of seizures or progressive neurological disease.

[ 22 ] ☐ Previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | | _____ |

# GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions, signs or symptoms present prior to the start of the study?

☐ No ☐ Yes → Please give diagnosis and tick (✓) appropriate Past/Current box(es).

| MedDRA SYSTEM ORGAN CLASS | DIAGNOSIS | PAST | CURRENT |
|---|---|---|---|
| [1] **Skin and subcutaneous tissue** | | ☐ ☐ | ☐ ☐ |
| [2] **Musculoskeletal and connective tissue** | | ☐ ☐ | ☐ ☐ |
| [3] **Cardiac** | | ☐ | ☐ |
| [4] **Vascular** | | ☐ | ☐ |
| [5] **Respiratory, thoracic and mediastinal** | | ☐ ☐ | ☐ ☐ |
| [6] **Gastrointestinal** | | ☐ | ☐ |
| [7] **Hepatobiliary** | | ☐ | ☐ |
| [8] **Renal and urinary** | | ☐ | ☐ |
| [9] **Nervous system** | | ☐ | ☐ |
| [10] **Eye** | | ☐ | ☐ |
| [11] **Ear and labyrinth** | | ☐ | ☐ |
| [12] **Endocrine** | | ☐ | ☐ |
| [13] **Metabolism and nutrition** | | ☐ | ☐ |
| [14] **Blood and lymphatic system** | | ☐ | ☐ |
| [15] **Immune system** (incl allergies, autoimmune disorders) | | ☐ ☐ | ☐ ☐ |
| [16] **Infections and infestations** | | ☐ | ☐ |
| [17] **Neoplasms benign, malignant and unspecified** (incl cysts, polyps) | | ☐ ☐ | ☐ ☐ |
| [18] **Surgical and medical procedures** | | ☐ | ☐ |
| [99] **Other** | | ☐ ☐ | ☐ ☐ |

Please report medication(s) as specified in the Epoch and fill in the **Medication** section.

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GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | | \|__\|__\|__\|__\|__\|__\| |

## VITAL SIGNS

Height: |__|__|__| cm

Weight: |__|__|__| . |__| kg

Gestational age |__|__|.|__| weeks

## LABORATORY TESTS (Only for Immunogenicity sub-cohort 1 and 2)

**SERUM SAMPLE** [SER]
(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__|
day month year

→ Clearstone Accession Number *: |__|__|__|__|__|__|__|__|__|__|

☐ No

* **Please prefix Clearstone Accession Number with "C"**

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**CONFIDENTIAL**

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | **Immunogenicity Sub-cohort 1 and Non Immunogenicity cohort** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|.|__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vaccine intake interrupted due to vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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CONFIDENTIAL

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|. |__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

Has **OPV Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

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CONFIDENTIAL

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 1** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## VACCINE ADMINISTRATION (continued)

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:

[I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

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CONFIDENTIAL - DRAFT

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **DOSE 1** | | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 7?

[N] ☐ No
[Y] ☐ Yes, please tick No/Yes for each sign/symptom and complete further as necessary.
[U] ☐ Unknown, no information available
[NA] ☐ Not applicable, no vaccine administered.

Record temperatures if during the solicited period at least one oral/axillary/tympanic measure is above or equal to 37.1 °C or at least one rectal (or tympanic-rectal conversion) measure is above or equal to 37.6°C.

| **Temperature [TE]**<br>≥ 37.1 °C [A/O/T/TO]<br>≥ 37.6 °C [R/TR]<br>☐ No<br>☐ Yes → °C<br>☐ Not Taken | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **After Day 7**<br>If ongoing, record **maximum temperature** and **end date** | | | **Rel. to inv. Product** | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | __._ | __._ | __._ | __._ | __._ | __._ | __._ | __._ | Ongoing | **Max** Temp. | ✓ box if continuing at end of study ↓ | | |
| | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ Not Taken | ☐ No<br>☐ Yes → | ___._ | \|__\|__\|__\|__\|__\|__\|__\|__\|__\|__\| or ☐ | ☐ No<br>☐ Yes | NO/HO/ER/MD<br>\|__\|__\| |

Route: [A] ☐ Axillary (armpit) (Preferred)
[O] ☐ Oral
[R] ☐ Rectal

[T] ☐ Tympanic
↳ conversion:
[T] ☐ none (or unknown)
[TO] ☐ oral conversion
[TR] ☐ rectal conversion

| **Intensity**: 0 / 1 / 2 / 3<br>*(see Adverse Events definitions)* | **Relationship to investigational product**:<br>Is there a reasonable possibility that the AE may have been caused by the investigational product. | **Medically attended visit**:<br>*(see protocol for full definition)*<br>NO: None<br>HO: Hospitalization<br>ER: Emergency Room<br>MD: Medical Personnel |
|---|---|---|

If any of these adverse events meets the definition of **serious**, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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CONFIDENTIAL - DRAFT

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **DOSE 1** | **Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (continued)

| General sign / symptom | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day6 | Day7 | After Day 7: Ongoing | After Day 7: Max intensity | After Day 7: Date of last day of sign/symptoms day month year | Rel. to inv. Product | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/Fussiness** [IR] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|‖\|__\|__\|‖\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|‖\|__\|__\|‖\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Cough/runny nose** [CO] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|‖\|__\|__\|‖\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Diarrhea** [DA] ☐ No ☐ Yes → Record the number of looser than normal stools /day | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|‖\|__\|__\|‖\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Vomiting** [VO] ☐ No ☐ Yes → Record the number of vomiting episodes/day | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|‖\|__\|__\|‖\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |

**Intensity:** 0 / 1 / 2 / 3 *see Adverse Events definitions)*

**Relationship to investigational product:** Is there a reasonable possibility that the AE may have been caused by the investigational product.

**Medically attended visit:** *(see protocol for full definition)*
NO: None ER: Emergency Room
HO: Hospitalization MD: Medical Personnel

**Stool sample should be collected in case of diarrhea according to protocol which is 3 or more looser than normal stools per day**

**Stool Collection:** Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|__|

**If diarrhea, please complete the following items:**

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify: _____

**(*) Please prefix Clearstone Accession Number with "C"**

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.**

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CONFIDENTIAL - DRAFT

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **DOSE 1** | **Immunogenicity Sub-cohort 2** | _____ |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (continued)

| General sign / symptom | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day6 | Day7 | After Day 7: Ongoing | After Day 7: Max intensity | After Day 7: Date of last day of sign/symptoms day month year | Rel. to inv. Product | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness** [IR] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __ __ \|\| __ __ \|\| ____ or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD __ |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __ __ \|\| __ __ \|\| ____ or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD __ |
| **Drowsiness** [DR] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __ __ \|\| __ __ \|\| ____ or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD __ |
| **Gastrointestinal symptoms** † [GI] ☐ No ☐ Yes → intensity: | __ | __ | __ | __ | __ | __ | __ | __ | ☐ No ☐ Yes → | __ | ✓ box if continuing at end of study ↓ __ __ \|\| __ __ \|\| ____ or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD __ |

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain.

| **Intensity:** | **Relationship to investigational product:** | **Medically attended visit:** *(see protocol for full definition)* | | | |
|---|---|---|---|---|---|
| 0 / 1 / 2 / 3 | Is there a reasonable possibility that the AE may have been caused | NO: | None | ER: | Emergency Room |
| *see Adverse Events definitions)* | by the investigational product. | HO: | Hospitalization | MD: | Medical Personnel |

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours**.

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**VISIT 2**

**MONTH 1**

CONFIDENTIAL

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | | \|__\|__\|__\|__\|__\|__\| |

## CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or Solicited AE Code |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | ___ ___ ____ (day month year) | _____ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 1 AND NON-IMMUNOGENICITY SUB-COHORT**

Did the subject present GE from Day 8 after Dose 1 of HRV vaccine or Placebo until Visit 2?

OR

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 1 to Visit 2?

☐ No

☐ Yes, If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|.|__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: ––––––––––––––––––––––––––––

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__| or solicited AE code |__|__|

[OTH] ☐ Other, please specify: ––––––––––––––––––––––––––––

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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CONFIDENTIAL

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|.|__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [To] ☐ oral conversion
    - [Tr] ☐ rectal conversion

Has **HRV Vaccine** or placebo been administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: ----------

***Oral vaccine intake characteristics (tick only one box):***

- ☐ Smooth vaccine intake
- ☐ Vaccine intake interrupted due to coughing or choking
- ☐ Regurgitation after vaccine intake (**)
- ☐ Vomiting after vaccine intake (**)

(**) If regurgitation or vomiting occurs after vaccination, do not give another dose at this visit

Has **OPV Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: ----------

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION (continued)

Has **DTPa Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number: \|__\|__\|__\|__\|__\|__\|

→ Injection Site / Side / Route:

☐ According to protocol: Anterolateral Thigh - Left - IM

☐ Not according to protocol,
specify Site: [1] ☐ Deltoid [3] ☐ Thigh [6] ☐ Buttock
Side: [L] ☐ Left [R] ☐ Right
Route: [IM] ☐ I.M. [SC] ☐ S.C.

→ *if relevant*, comment on administration: _____

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. \|__\|__\|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. \|__\|__\| or solicited AE code \|__\|__\|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

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CONFIDENTIAL - DRAFT

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**113808 (Rota-075)**

| | | | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - LOCAL SIGNS/SYMPTOMS

### DTPa vaccine injection site

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 7?

[N] ☐ No
[Y] ☐ Yes, please tick No/Yes for each sign/symptom and complete further as necessary.
[U] ☐ Unknown, no information available
[NA] ☐ Not applicable, no vaccine administered.

| **Local sign / symptom** | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day6** | **Day7** | **After Day 7** Ongoing | Max Intensity/ Size | Date of last day of sign/symptoms day month year | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Redness** [RE]<br>☐ No<br>☐ Yes → size (mm): | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No<br>☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓<br>\|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | NO/HO/ER/MD<br>\|_\|_\| |
| **Swelling** [SW]<br>☐ No<br>☐ Yes → size (mm): | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No<br>☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓<br>\|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | NO/HO/ER/MD<br>\|_\|_\| |
| **Pain** [PA]<br>☐ No<br>☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No<br>☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓<br>\|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | NO/HO/ER/MD<br>\|_\|_\| |

**Intensity:**
0 / 1 / 2 / 3
*see Adverse Events definitions)*

**Medically attended visit:** *(see protocol for full definition)*
NO: None ER: Emergency Room
HO: Hospitalization MD: Medical Personnel

If any of these adverse events meets the definition of **serious**, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

Has the subject experienced any of the following signs/symptoms between Day 0 and Day 7?

[N] ☐ No
[Y] ☐ Yes, please tick No/Yes for each sign/symptom and complete further as necessary.
[U] ☐ Unknown, no information available
[NA] ☐ Not applicable, no vaccine administered.

Record temperatures if during the solicited period at least one oral/axillary/tympanic measure is above or equal to 37.1 °C or at least one rectal (or tympanic-rectal conversion) measure is above or equal to 37.6°C.

| **Temperature [TE]**<br>≥ 37.1 °C [A/O/T/TO]<br>≥ 37.6 °C [R/TR]<br>☐ No<br>☐ Yes → °C<br>☐ Not Taken | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **After Day 7**<br>If ongoing, record **maximum temperature** and **end date** | | | **Rel. to inv. Product** | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | __.__ ☐ Not Taken | __.__ ☐ Not Taken | __.__ ☐ Not Taken | __.__ ☐ Not Taken | __.__ ☐ Not Taken | __.__ ☐ Not Taken | __.__ ☐ Not Taken | __.__ ☐ Not Taken | Ongoing | **Max** Temp. | ✓ box if continuing at end of study ↓ | | |
| | | | | | | | | | ☐ No<br>☐ Yes → | ___.__ | \|__\|__\|__\|__\|__\|__\| or ☐ | ☐ No<br>☐ Yes | NO/HO/ER/MD<br>\|__\|__\| |

Route: [A] ☐ Axillary (armpit) (Preferred)
[O] ☐ Oral
[R] ☐ Rectal
[T] ☐ Tympanic
↳ conversion:
[T] ☐ none (or unknown)
[TO] ☐ oral conversion
[TR] ☐ rectal conversion

| **Intensity**: 0 / 1 / 2 / 3<br>*(see Adverse Events definitions)* | **Relationship to investigational product**:<br>Is there a reasonable possibility that the AE may have been caused by the investigational product. | **Medically attended visit**:<br>*(see protocol for full definition)*<br>NO: None<br>HO: Hospitalization<br>ER: Emergency Room<br>MD: Medical Personnel |
|---|---|---|

If any of these adverse events meets the definition of **serious**, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.

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GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS (continued)

| General sign / symptom | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day6 | Day7 | After Day 7: Ongoing | After Day 7: Max intensity | After Day 7: Date of last day of sign/symptoms day month year | Rel. to inv. Product | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/Fussiness** [IR] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Cough/runny nose** [CO] ☐ No ☐ Yes → intensity: | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Diarrhea** [DA] ☐ No ☐ Yes → Record the number of looser than normal stools /day | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Vomiting** [VO] ☐ No ☐ Yes → Record the number of vomiting episodes/day | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | \|___\| | ☐ No ☐ Yes → | \|___\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |

**Intensity**:
0 / 1 / 2 / 3
*see Adverse Events definitions)*

**Relationship to investigational product**:
Is there a reasonable possibility that the AE may have been caused by the investigational product.

**Medically attended visit**: *(see protocol for full definition)*
NO: None ER: Emergency Room
HO: Hospitalization MD: Medical Personnel

**Stool sample should be collected in case of diarrhea according to protocol which is 3 or more looser than normal stools per day**

**Stool Collection:** Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|__|

Stool collection date: |__|__| |__|__|__| |__|__|__|__| hour: |__|__| min: |__|__| Clearstone Accession Number **(*)**:|__|__|__|__|__|__|__|__|__|

**If diarrhea, please complete the following items:**

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify: _____

**(*) Please prefix Clearstone Accession Number with "C"**

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.**

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GlaxoSmithKline

**113808 (Rota-075)**

| | | | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 2** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## SOLICITED ADVERSE EVENTS - GENERAL SIGNS/SYMPTOMS

| **General sign / symptom** | **Day 0** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day6** | **Day7** | **After Day 7** Ongoing | Max intensity | Date of last day of sign/symptoms day month year | **Rel. to inv. Product** | **Medically attended visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness** [IR] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Loss of appetite** [LO] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Drowsiness** [DR] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |
| **Gastrointestinal symptoms** † [GI] ☐ No ☐ Yes → intensity: | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | \|__\| | ☐ No ☐ Yes → | \|__\| | ✓ box if continuing at end of study ↓ \|__\|__\|\|__\|__\|\|__\|__\|__\|__\| or ☐ | ☐ No ☐ Yes | NO/HO/ER/MD \|_\|_\| |

†Gastrointestinal symptoms include nausea, vomiting, diarrhea and/or abdominal pain. These AEs are specific to OPV.

| **Intensity:** | **Relationship to investigational product:** | **Medically attended visit:** *(see protocol for full definition)* |
|---|---|---|
| 0 / 1 / 2 / 3 *see Adverse Events definitions)* | Is there a reasonable possibility that the AE may have been caused by the investigational product. | NO: None ER: Emergency Room HO: Hospitalization MD: Medical Personnel |

**If any of these adverse events meets the definition of serious, complete and submit a Serious Adverse Event report to GSK Biologicals Study Contact for SAE reporting within 24 hours.**

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**VISIT 3**

**MONTH 2**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

☐ [SAE] Serious adverse event:

→ Please complete and submit **SAE** report.

→ Please specify SAE Case No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section

→ Please specify AE No. |__|__| Or solicited AE code: |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [SST] Sponsor study termination.

☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year | \|__\|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 1 AND NON-IMMUNOGENICITY SUB-COHORT**

Did the subject present GE from Day 8 after Dose 2 of HRV vaccine or Placebo until Visit 3?

OR

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 2 to Visit 3?

☐ No

☐ Yes …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

## LABORATORY TESTS (only for subjects in Immunogenicity sub-cohort 1 and 2)

### SERUM SAMPLE [SER]

(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: |__|__| |__|__|__| |__|__|__|__| day month year

→ Clearstone Accession Number *: |__|__|__|__|__|__|__|__|__|__|

☐ No

* **Please prefix Clearstone Accession Number with "C"**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: |__|__| |__|__|__| |__|__|__|__|
(if different from visit date) day month year

Pre-Vaccination temperature: |__|__|. |__| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **OPV Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number : |__|__|__|__|__|__|

→ Route:
- ☐ According to protocol: ORAL
- ☐ Not according to protocol

→ *if relevant*, comment on administration: _____

Has **DTPa Vaccine** been co-administered?

[N] ☐ No → Please give reason below.

[Y] ☐ Yes → Administered Treatment Number: |__|__|__|__|__|__|

→ Injection Site / Side / Route:

☐ According to protocol: Anterolateral Thigh - Left - IM

☐ Not according to protocol,
specify Site: [1] ☐ Deltoid [3] ☐ Thigh [6] ☐ Buttock
Side: [L] ☐ Left [R] ☐ Right
Route: [IM] ☐ I.M. [SC] ☐ S.C.

→ *if relevant*, comment on administration: _____

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 3** | **Immunogenicity Sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION (continued)

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

[SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report

→ Please specify SAE Case No. |__|__|

[AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section

→ Please specify AE No. |__|__| Or solicited AE code: |__|__|

[OTH] ☐ Other, please specify: _____

(e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

**Note: Please report any non-serious AE that lead to withdrawal**

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**VISIT 4**

**MONTH 3**

## Only for subjects in sub-cohort 2

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 4** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or solicited AE code: |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 4** | __ __ day __ __ month __ __ __ __ year | _____ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 3 to Visit 4?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 4** | | \|__\|__\|__\|__\|__\|__\| |

# VACCINE ADMINISTRATION

Date of administration: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
(if different from visit date) day month year

Pre-Vaccination temperature: \|__\|__\|. \|__\| °C

Route:
- [A] ☐ Axillary (Preferred)
- [O] ☐ Oral
- [R] ☐ Rectal
- [T] ☐ Tympanic
  - conversion:
    - [T] ☐ none (or unknown)
    - [TO] ☐ oral conversion
    - [TR] ☐ rectal conversion

Has **DTPa Vaccine** been co-administered?

- [N] ☐ No → Please give reason below.
- [Y] ☐ Yes → Administered Treatment Number: \|__\|__\|__\|__\|__\|__\|
  - → Injection Site / Side / Route:
    - ☐ According to protocol: Anterolateral Thigh - Left - IM
    - ☐ Not according to protocol,
      specify Site: [1] ☐ Deltoid [3] ☐ Thigh [6] ☐ Buttock
      Side: [L] ☐ Left [R] ☐ Right
      Route: [IM] ☐ I.M. [SC] ☐ S.C.
  - → *if relevant*, comment on administration: _____

***If no vaccination,***

→ Please tick (✓) the major reason for non administration

- [SAE] ☐ Serious Adverse Event: → Please complete and submit SAE report
  - → Please specify SAE Case No. \|__\|__\|
- [AEX] ☐ Non-Serious Adverse Event: → Please complete Non-Serious Adverse Event section
  - → Please specify AE No. \|__\|__\| Or solicited AE code: \|__\|__\|
- [OTH] ☐ Other, please specify: _____
  (e.g.: consent withdrawal, Protocol violation, …)

→ Please tick (✓) who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

**Note: Please report any non-serious AE that lead to withdrawal**

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**VISIT 5**

**MONTH 4**

## Only for subjects in sub-cohort 2

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 5** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for this visit?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

☐ [SAE] Serious adverse event:

→ Please complete and submit **SAE** report.

→ Please specify SAE Case No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section

→ Please specify AE No. |__|__| Or solicited AE code: |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [SST] Sponsor study termination.

☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

→ **Study discontinuation**

☐ [Y] Tick box *only if permanent discontinuation*, i.e. if the subject definitively withdraws from the study

In this case, terminate the CRF:

Complete Medication, Concomitant Vaccination, (S)AE sections and End of Epoch(s) (Study Conclusion) as appropriate

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 5** | __ __ day __ __ __ month __ __ __ __ year | _____ |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 4 to Visit 5?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

## LABORATORY TESTS

**SERUM SAMPLE** [SER]
(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: __ __ day __ __ __ month __ __ __ __ year

→ Clearstone Accession Number *: _____

☐ No

* **Please prefix Clearstone Accession Number with "C"**

**Note: Please report any non-serious AE that lead to withdrawal**

**VISIT 6**
**YEAR 1 OF AGE**
**EFFICACY**
**FOLLOW-UP**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 6** | | \|__\|__\|__\|__\|__\|__\| |

# CHECK FOR STUDY CONTINUATION

Did the subject return for the visit 6?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

☐ [SAE] Serious adverse event:

→ Please complete and submit **SAE** report.

→ Please specify SAE Case No. |__|__|

☐ [AEX] Non-Serious adverse event:

→ Please complete **Non-serious Adverse Event** section

→ Please specify AE No. |__|__| Or solicited AE code: |__|__|

☐ [PTV] Protocol violation, please specify: _____

☐ [CWS] Consent withdrawal, not due to an adverse event

☐ [MIG] Migrated / moved from the study area

☐ [LFU] Lost to follow-up.

☐ [SST] Sponsor study termination.

☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision: [I] ☐ Investigator

[P] ☐ Parents/Legally Acceptable Representatives

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**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 6** | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year | \|__\|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODES

**FOR SUBJECTS IN SUB-COHORT 1 AND NON-IMMUNOGENICITY SUB-COHORT**

Did the subject present GE between Visit 3 to visit 6?

OR

**FOR SUBJECTS IN SUB-COHORT 2**

Did the subject present GE from Visit 5 to Visit 6?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

## LABORATORY TESTS (only for immunogenicity sub-cohort 1 and 2)

### SERUM SAMPLE [SER]

(Bio specimen Label = SERUM)

Has a serum sample been taken?

☐ Yes → Date if different from visit date: |__\|__\| |__\|__\|__\| |__\|__\|__\|__\| day month year

→ Clearstone Accession Number *: |__\|__\|__\|__\|__\|__\|__\|__\|__\|__\|

☐ No

* **Please prefix Clearstone Accession Number with "C"**

**Note: Please report any non-serious AE that lead to withdrawal**

**POST VISIT 6**
**INFORMED CONSENT**

# An additional Informed Consent has to be obtained prior to any study procedure related to follow up period between visit 6 and visit 7

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **POST VISIT 6** | | \|__\|__\|__\|__\|__\|__\| |

## INFORMED CONSENT

Did the subject's parents/LAR sign the informed consent to participate in the follow up period between visit 6 and visit 7?

☐ No

☐ Yes → please fill the **informed consent date** \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

☐ NA

**Reminder:**

- 'Yes' should be answered if the Protocol Amendment 2 has been approved and the subject signed the informed consent to participate in the follow up period between visit 6 and visit 7.
- 'No' should be answered if the Protocol Amendment 2 has been approved and the subject did not sign the informed consent to participate in the follow up period between visit 6 and visit 7.
- 'NA' should be answered if the Protocol Amendment was not approved.

**VISIT 7**

**EFFICACY**

**FOLLOW-UP**

**Only for subjects whose parents//LAR have signed the Informed Consent to participate in the follow up period between visit 6 and visit 7**

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**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **VISIT 7** | | \|__\|__\|__\|__\|__\|__\| |

## CHECK FOR STUDY CONTINUATION

Did the subject return for the visit 7?

☐ Yes → *Go to next page*

---

☐ No → **Major reason.** Tick 1 box, major reason only:

- ☐ [SAE] Serious adverse event:
  - → Please complete and submit **SAE** report.
  - → Please specify SAE Case No. |__|__|
- ☐ [AEX] Non-Serious adverse event:
  - → Please complete **Non-serious Adverse Event** section
  - → Please specify AE No. |__|__| Or solicited AE code: |__|__|
- ☐ [PTV] Protocol violation, please specify: _____
- ☐ [CWS] Consent withdrawal, not due to an adverse event
- ☐ [MIG] Migrated / moved from the study area
- ☐ [LFU] Lost to follow-up.
- ☐ [SST] Sponsor study termination.
- ☐ [OTH] Other, please specify: _____

→ For *serious (excepting death)*, *non-serious adverse events* and *Other* reasons only:

Who made the decision:
- [I] ☐ Investigator
- [P] ☐ Parents/Legally Acceptable Representatives

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GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | Date of visit | Subject Number |
|---|---|---|---|---|
| | | **VISIT 7** | __ __ day __ __ __ month __ __ __ __ year | __ __ __ __ __ __ |

## GASTROENTERITIS EPISODES

**FOR ALL COHORTS**

Did the subject present GE from Visit 6 to Visit 7?

☐ No

☐ Yes, …If yes → please fill the **Gastroenteritis Episodes** section

→ please collect a stool sample as soon as possible after diarrhea begins and preferably not later than 7 days after the start of the diarrhea and report the stool collection date in the **Gastroenteritis Episodes** section.

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# GASTROENTERITIS EPISODES VISIT 1 TO VISIT 7

CONFIDENTIAL

**113808 (Rota-075)**

| | | | | Subject Number |
|---|---|---|---|---|
| | | | | \|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 7

**EPISODE N°**: |__|__|

Treatment?
☐ No
☐ Yes →
- ☐ Oral rehydration
- ☐ IV rehydration
- ☐ Oral and IV rehydration
- ☐ Other, please specify: __________________________

Medical advice:
- ☐ Medical doctor
- ☐ Emergency room
- ☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (**)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

**(*) Please prefix Clearstone Accession Number with "C"**

**(**) Route: axillary is mandatory.**

| | | | | Subject Number |
|---|---|---|---|---|
| | | | | \|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 7

**EPISODE N°**: |__|__|

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|

<table>
<tr><th>Date<br>day month year</th><th>Number of looser than normal stools per day</th><th>Number of vomiting per day</th><th>Temperature (°C) → route:</th><th>☐ Axillary (**)<br>☐ Oral<br>☐ Rectal</th></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__| . |__|</td><td>☐ not taken</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__| . |__|</td><td>☐ not taken</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__| . |__|</td><td>☐ not taken</td></tr>
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<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__| . |__|</td><td>☐ not taken</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__| . |__|</td><td>☐ not taken</td></tr>
<tr><td>|__|__| |__|__|__| |__|__|__|__|</td><td>|__|__|</td><td>|__|__|</td><td>|__|__| . |__|</td><td>☐ not taken</td></tr>
</table>

**(*) Please prefix Clearstone Accession Number with “C”**

(**) **Route: axillary is mandatory.**

| | | | | Subject Number |
|---|---|---|---|---|
| | | | | \|__\|__\|__\|__\|__\|__\| |

## GASTROENTERITIS EPISODE FROM VISIT 1 TO VISIT 7

**EPISODE N°**: |__|__|

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: __________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Clearstone Accession Number (*): |__|__|__|__|__|__|__|__|__|__|

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C)** → **route:** | ☐ **Axillary** (**)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\| . \|__\| | ☐ not taken |

**(*) Please prefix Clearstone Accession Number with “C”**

**(**) Route: axillary is mandatory.**

**CONCOMITANT VACCINATION VISIT 1 TO VISIT 7**

| | | | | |
|---|---|---|---|---|
| | | Visit | | Subject Number |
| | | **CONCOMITANT VACCINATION** | | \|__\|__\|__\|__\|__\|__\| |

# CONCOMITANT VACCINATION

Have any vaccines other than the study vaccine(s) been administered during the time frame as specified in the protocol?

☐ No

☐ Yes → Please complete the following table.

| **Trade / (Generic) Name** | **Route** | **Administration date**<br>**day month year** |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| |
| **For GSK** | | |

**Route:**

| | | | |
|---|---|---|---|
| ID | = Intradermal | PE | = Parenteral |
| IH | = Inhalation | PO | = Oral |
| IM | = Intramuscular | SC | = Subcutaneous |
| IN | = Intranasal | SL | = Sublingual |
| IV | = Intravenous | TD | = Transdermal |
| OTH | = Other | UNK | = Unknown |

***Previous vaccination against DTPa and OPV should be reported in the CRF***

# MEDICATION
# VISIT 1 TO VISIT 7

**ROUTE**

| Code | Label |
|---|---|
| ID | Intradermal |
| IH | Inhalation |
| IM | Intramuscular |
| IN | Intranasal |
| IR | Intraarticular |
| IV | Intravenous |
| PE | Parenteral |
| PO | Oral |
| PR | Rectal |
| SC | Subcutaneous |
| SL | Sublingual |
| TD | Transdermal |
| TO | Topical |
| VA | Vaginal |
| OTH | Other |
| UNK | Unknown |

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**113808 (Rota-075)**

<table>
<tr><td></td><td></td><td>Visit</td><td></td><td>Subject Number</td></tr>
<tr><td></td><td></td><td>MEDICATION</td><td></td><td>|__|__|__|__|__|__|</td></tr>
</table>

# MEDICATION

Have any medications been administered during the time frame as specified in the protocol?

☐ No
☐ Yes → Please complete the following table.

<table>
<tr><th rowspan="2">Trade / Generic Name</th><th rowspan="2">Medical Indication</th><th colspan="2">Total daily dose</th><th rowspan="2">Route<br>Use codes given on pre bvious page</th><th rowspan="2">Start Date day/month/year<br>End Date day/month/year<br>or ✓ box if continuing at end of study ↓</th></tr>
<tr><th>Dose</th><th>Unit</th></tr>
<tr><td><br>For GSK use only</td><td>☐ in anticipation of study vaccine reaction<br>☐ chronic use</td><td></td><td></td><td></td><td>Start: |__|__||__|__|__||__|__|__|__|<br>End: |__|__||__|__|__||__|__|__|__| or ☐</td></tr>
<tr><td><br>For GSK use only</td><td>☐ in anticipation of study vaccine reaction<br>☐ chronic use</td><td></td><td></td><td></td><td>Start: |__|__||__|__|__||__|__|__|__|<br>End: |__|__||__|__|__||__|__|__|__| or ☐</td></tr>
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</table>

**NON-SERIOUS ADVERSE EVENT VISIT 1 TO VISIT 7**

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL** | **Immunogenicity sub-cohort 1 and Non-immunogenicity cohort** | \|__\|__\|__\|__\|__\|__\| |

## NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS

**(Please report *serious* adverse events only in the Serious Adverse Event report, not here)**

Have any non-serious adverse events/intercurrent medical conditions occurred during the time frame as specified in the protocol?

☐ No
☐ Yes → Please complete the following table.

| # | Event | Start date<br>Tick (✓) if 30 min immediate post-vaccination ↓ | | Outcome | End date | Maximum intensity | Relationship to investigational product(s) | Medically attended visit |
|---|---|---|---|---|---|---|---|---|
| | Diagnosis only (if known), otherwise sign / symptom | Day Month Year (DD MMM YYYY) | 30min post vacc | 1: Recovered/ Resolved<br>2: Recovering / Resolving<br>3: Not recovered/ Not resolved<br>4: Recovered/ Resolved with sequelae | Day Month Year (DD MMM YYYY) | 1: Mild<br>2: Moderate<br>3: Severe | Is there a reasonable possibility that the AE may have been caused by the investigational product?<br>Y=Yes N=No | **NO**:None<br>**HO**: Hospitalisation<br>**ER**: Emergency Room<br>**MD**:Medical Personnel<br>Refer to protocol for full definition |
| 1 | For GSK use only | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 2 | For GSK use only | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 3 | For GSK use only | \|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\| | | | |

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GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL** | **Immunogenicity sub-cohort 2** | \|__\|__\|__\|__\|__\|__\| |

## NON-SERIOUS ADVERSE EVENTS AND INTERCURRENT MEDICAL CONDITIONS

**(Please report *serious* adverse events only in the Serious Adverse Event report, not here)**

Have any non-serious adverse events/intercurrent medical conditions occurred during the time frame as specified in the protocol?

☐ No
☐ Yes → Please complete the following table.

| # | Event | Site | Start date<br>Tick (✓) if 30 min immediate post-vaccination ↓ | | Outcome | End date | Maximum intensity | Relationship to investigational product(s) | Medically attended visit |
|---|---|---|---|---|---|---|---|---|---|
| | Diagnosis only (if known), otherwise sign / symptom | | Day Month Year (DD MMM YYYY) | 30min post vacc | 1: Recovered/ Resolved<br>2: Recovering / Resolving<br>3: Not recovered/ Not resolved<br>4: Recovered/ Resolved with sequelae | Day Month Year (DD MMM YYYY) | 1: Mild<br>2: Moderate<br>3: Severe | Is there a reasonable possibility that the AE may have been caused by the investigational product? Y=Yes N=No | **NO**:None<br>**HO**: Hospitalisation<br>**ER**: Emergency Room<br>**MD**:Medical Personnel<br>Refer to protocol for full definition |
| 1 | For GSK use only | ☐ Non-Administration site<br>☐ Administration site | \|__\|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 2 | For GSK use only | ☐ Non-Administration site<br>☐ Administration site | \|__\|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\|__\| | | | |
| 3 | For GSK use only | ☐ Non-Administration site<br>☐ Administration site | \|__\|__\|__\|__\|__\|__\|__\|__\|__\| | ☐ | | \|__\|__\|__\|__\|__\|__\|__\|__\|__\| | | | |

**STUDY CONCLUSION**

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **STUDY CONCLUSION** | | \|__\|__\|__\|__\|__\|__\| |

# STUDY CONCLUSION

## LAST INFORMATION

Date of last contact or

date when the last information was collected on the subject's condition: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Was the subject in good condition at this date?

☐ Yes

☐ No → Give details in serious or non-serious adverse events section.

## OCCURRENCE OF SERIOUS ADVERSE EVENT

Did the subject experience any Serious Adverse Event since the start of the study?

☐ No

☐ Yes → Check SAE report(s) have been submitted

GlaxoSmithKline

**113808 (Rota-075)**

| | | Visit | | Subject Number |
|---|---|---|---|---|
| | | **CONCLUSION** | | \|__\|__\|__\|__\|__\|__\| |

## INVESTIGATOR'S SIGNATURE

I confirm that I have reviewed the data in this Case Report Form for this subject. All information entered by myself or my colleagues is, to the best of my knowledge, complete and accurate, as of the date below.

Investigator's signature: _____ Date: |__|__| |__|__|__| |__|__|__|__|
day month year

Printed Investigator's name: _____

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GlaxoSmithKline

**113808 [ROTA-075]**

| | | | Centre No. | UHS form version |
|---|---|---|---|---|
| | | | \|__\|__\|__\|__\|__\|__\|__\| | \|__\| |

## USE OF HUMAN SAMPLES BY GSK

**In addition to the tests described in the study protocol, please check what may also be done with the subject samples as per the Informed Consent Form (ICF) in use at your center.**

☐ Yes ☐ No [type 3a tests] Use of samples to improve, develop or assess tests related to the disease(s) or the vaccine(s)/product(s) under study that will allow more reliable measurement of the vaccine/product response. This excludes testing related to genes' hereditary characteristics and HIV

☐ Yes ☐ No [type 3b tests] ***With the prior permission of the institution independent Ethics Committee / Institutional Review Board:***

Use of samples to improve, develop or assess tests related to the disease(s) or the vaccine(s)/product(s) under study that will allow more reliable measurement of the vaccine/product response. This excludes testing related to genes' hereditary characteristics and HIV

☐ Yes ☐ No [type 4 tests] ***With the prior permission of the subject:***

Further research by GSK Biologicals that is NOT RELATED to the disease(s) or the vaccine(s)/product(s) under study. This research is done on an anonymous basis (any identification linking the subject to the sample is destroyed), excludes testing related to genes' hereditary characteristics and HIV, and does not affect the subject participation in the study.

**Please check GSK Biologicals sample storage period specified in the ICF in use at your center.**

☐ up to 15 years

☐ Other, specify: _____

**If new version of UHS:**

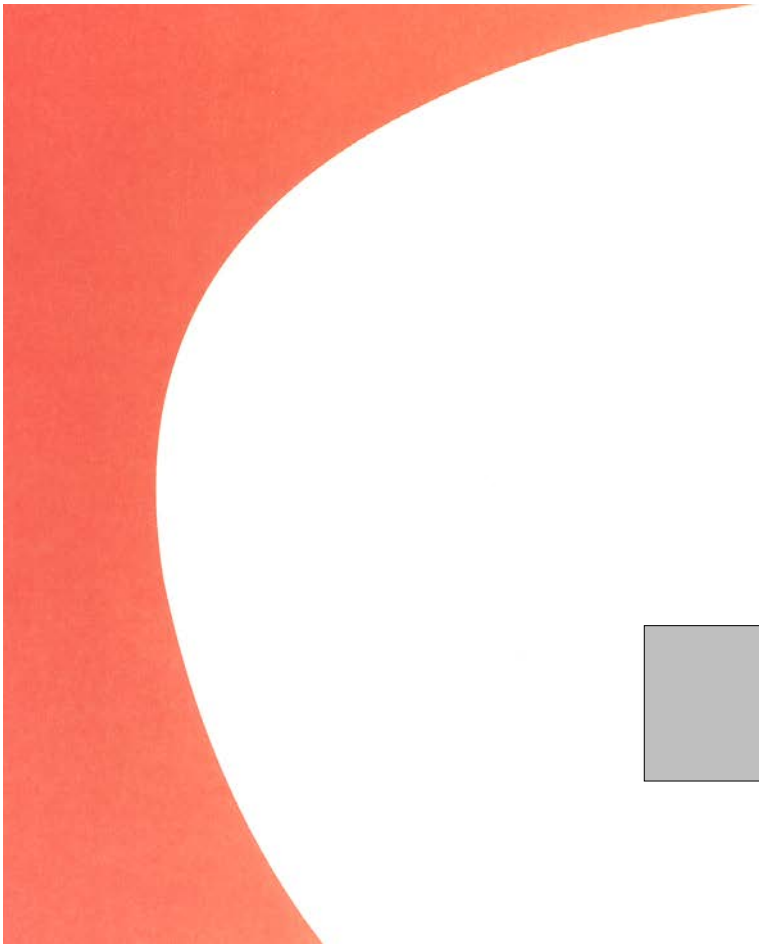
Date at which the new ICF version was first signed by a subject : |__|__| |__|__|__| |__|__|__|__|
day month year

Complete and submit a *new Use of Human Samples by GSK* form for each change in the ICF that affects the use of samples.

## INVESTIGATOR'S SIGNATURE

Investigator's signature: _____ Date: |__|__||__|__|__||__|__|__|__|
day month year

Printed Investigator's name: _____



GlaxoSmithKline

# *Diary Card*

***Subject number***

|__|__|__|__|__|__|__|

To be completed by the Investigator

## *Protocol 113808 (Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

Diary Card template13.1 – August 06, 2010

# VISIT 1

**Immunogenicity Sub-Cohort 1 and Non-Immunogenicity Cohort**

Diary Card template13.1 – August 06, 2010

CONFIDENTIAL

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 1** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |

## GENERAL SYMPTOMS

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: ≥37.1°C Axillary | After Day 7: Max Temperature | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No<br>☐ Yes → | °C | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\|__\| |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement:
(The same route must be used for all your measurements.)
☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: Ongoing | After Day 7: Max Intensity | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\|__\| |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\|__\| |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Cough/runny nose → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\|__\| |
| Intensity: **0**: Normal **1**: Cough/runny nose which is easily tolerated **2**: Cough/runny nose which interferes with daily activity **3**:Cough/runny nose which prevents daily activity | | | | | | | | | | | | | |
| **Diarrhea→** | | | | | | | | | ☐ No<br>☐ Yes → | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\|__\| |
| Record the number of looser than normal stools /day | | | | | | | | | | | | | |
| **Vomiting →** | | | | | | | | | ☐ No<br>☐ Yes → | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|__\|__\| |
| Record the number of vomiting episodes/day | | | | | | | | | | | | | |

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**Stool Collection:** Stool collection date: |__|__|____|_____| hour: |__| min: |__|

Stool collection date: |__|__|____|_____| hour: |__| min: |__|

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify:

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| 113808 (Rota-075) | **DIARY CARD** **Visit 1** | **Subject Number** \|__\|__\|__\|__\|__\|__\| To be completed by the investigator |
|---|---|---|

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |

**Route:**

| | | | |
|---|---|---|---|
| ID | = Intradermal | PE | = Parenteral |
| IH | = Inhalation | PO | = Oral |
| IM | = Intramuscular | SC | = Subcutaneous |
| IN | = Intranasal | SL | = Sublingual |
| IV | = Intravenous | TD | = Transdermal |
| OTH | = Other | UNK | = Unknown |

Diary Card template 13.1 – August 06, 2010

CONFIDENTIAL

| 113808 (Rota-075) | **DIARY CARD** **Visit 1** | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| Illness/Sign/Symptom | Max Intensity 1/2/3 | Start Date | End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

……

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template 13.1 – August 06, 2010

# VISIT 2

Diary Card template 13.1 – August 06, 2010

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD** Visit 2 | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: ≥37.1°C Axillary | After Day 7: Max Temperature | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No ☐ Yes → | °C | | ☐ No ☐ Yes | HO/ER/MD ___ |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement: (The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: Ongoing | After Day 7: Max Intensity | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Cough/runny nose → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Intensity: **0**: Normal **1**: Cough/runny nose which is easily tolerated **2**: Cough/runny nose which interferes with daily activity **3**:Cough/runny nose which prevents daily activity | | | | | | | | | | | | | |
| **Diarrhea→** | | | | | | | | | ☐ No ☐ Yes → | | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Record the number of looser than normal stools /day | | | | | | | | | | | | | |
| **Vomiting →** | | | | | | | | | ☐ No ☐ Yes → | | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Record the number of vomiting episodes/day | | | | | | | | | | | | | |

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**Stool Collection:** Stool collection date: |__|__|____|____| hour: |__| min: |__|

Stool collection date: |__|__|____|____| hour: |__| min: |__|

**Medication for diarrhea?** ☐ No ☐ Yes → ☐ Oral rehydration ☐ IV rehydration ☐ Oral and IV rehydration ☐ Other, please specify:

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| | | |
|---|---|---|
| 113808<br>(Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |

**Route:**

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IN = Intranasal
IV = Intravenous
OTH = Other
PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

Diary Card template 13.1 – August 06, 2010

| 113808 (Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| Illness/Sign/Symptom | Max Intensity 1/2/3 | Start Date | End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD __\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

……

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

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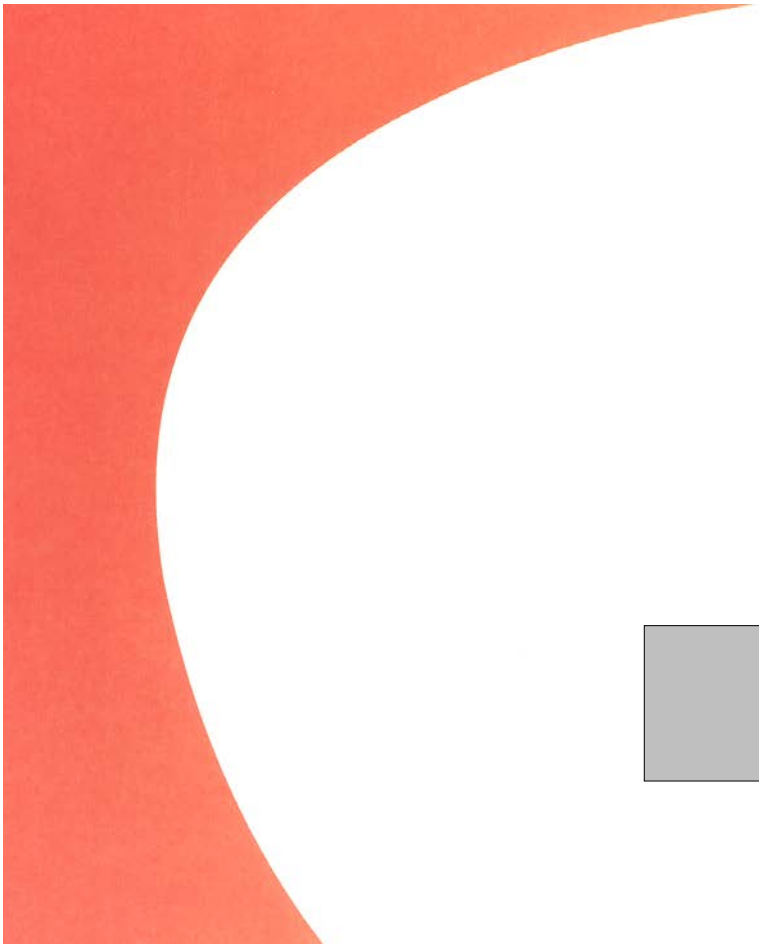

GlaxoSmithKline

# *Diary Card*

***Subject number***

|__|__|__|__|__|__|__|

To be completed by the Investigator

## *Protocol 113808 (Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

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# VISIT 1

**Immunogenicity Sub-Cohort 2**

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CONFIDENTIAL

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 1** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: ≥37.1°C Axillary | After Day 7: Max Temperature | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No<br>☐ Yes → | °C | | ☐ No<br>☐ Yes | HO/ER/MD<br>___ |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement:
(The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: Ongoing | After Day 7: Max Intensity | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>___ |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>___ |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Drowsiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>___ |
| Intensity: 0:Behaviour as usual 1: Mild: Drowsiness easily tolerated 2: Moderate: Drowsiness that interferes with normal activityactivity 3: Severe:Drowsiness that prevents normal activity | | | | | | | | | | | | | |
| **Gastrointestinal symptoms †→ intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No<br>☐ Yes → | 1/2/3 | | ☐ No<br>☐ Yes | HO/ER/MD<br>___ |
| Intensity: 0: Gastrointestinal symptoms normal 1: Mild: Gastrointestinal symptoms that are easily tolerated 2: Moderate: Gastrointestinal symptoms that interfere with normal activity 3: Severe:Gastrointestinal symptoms that prevent normal activity | | | | | | | | | | | | | |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

CONFIDENTIAL

| 113808 (Rota-075) | **DIARY CARD** **Visit 1** | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| Illness/Sign/Symptom | Max Intensity 1/2/3 | Start Date | End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |
| | | | | ☐ No ☐ Yes | HO/ER/MD _\|_\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

……

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010

# VISIT 2

| 113808 (Rota-075) | **DIARY CARD** Visit 2 | **Subject Number** \|__\|__\|__\|__\|__\|__\|__\|__\| To be completed by the investigator |
|---|---|---|

## LOCAL SYMPTOMS
## DTPa Vaccine

To be completed by the investigator:

**Date of vaccination = Day 0**: _____ **Injection Site**: _____ **Side**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7 Ongoing | After Day 7 Max Intensity | After Day 7 End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Injection site **Redness** → size (mm) | mm | mm | mm | mm | mm | mm | mm | mm | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Measure and record the greatest diameter (in mm). | | | | | | | | | | | | | |
| Injection site **Swelling** → size (mm) | mm | mm | mm | mm | mm | mm | mm | mm | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Measure and record the greatest diameter (in mm). | | | | | | | | | | | | | |
| Injection site **Pain** → intensity (0/1/2/3) | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ___ |
| Intensity: **0**:Absent **1**:Minor reaction to touch **2**:Cries/protests on touch **3**:Cries when limb is moved / spontaneously painful | | | | | | | | | | | | | |

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

| 113808 (Rota-075) | **DIARY CARD** Visit 2 | **Subject Number** \|___\|___\|___\|___\|___\|___\| To be completed by the investigator |
|---|---|---|

## GENERAL SYMPTOMS (OPV + DTPa VACCINE)

To be completed by the investigator: **Date of vaccination = Day 0**: _____

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: ≥37.1°C Axillary | After Day 7: Max Temperature | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Temperature →** | °C | °C | °C | °C | °C | °C | °C | °C | ☐ No ☐ Yes → | °C | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |

Record maximum temperature using provided thermometer. If axillary temperature is still ≥37.1°C or if rectal temperature is still ≥37.6°C after day 7, then provide also the maximum temperature measured during the following days.

Route of measurement: (The same route must be used for all your measurements.) ☐ Axillary (armpit)

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | After Day 7: Ongoing | After Day 7: Max Intensity | After Day 7: End Date | Did you receive medical attention?* | Type of medical attention To be completed by the investigator |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Irritability/ Fussiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: **0**:Behavior as usual **1**:Crying more than usual / no effect on normal activity **2**:Crying more than usual / interferes with normal activity **3**: Crying that cannot be comforted / prevents normal activity | | | | | | | | | | | | | |
| **Loss of appetite → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: **0**: Appetite as usual **1**: Eating less than usual/ no effect on normal activity **2**:Crying Eating less than usual/ interferes with normal activity **3**:Not eating at all | | | | | | | | | | | | | |
| **Drowsiness → intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: 0:Behaviour as usual 1: Mild: Drowsiness easily tolerated 2: Moderate: Drowsiness that interferes with normal activityactivity 3: Severe:Drowsiness that prevents normal activity | | | | | | | | | | | | | |
| **Gastrointestinal symptoms †→ intensity (0/1/2/3)** | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | 0/1/2/3 | ☐ No ☐ Yes → | 1/2/3 | | ☐ No ☐ Yes | HO/ER/MD ⌊⌋⌊⌋ |
| Intensity: 0: Gastrointestinal symptoms normal 1: Mild: Gastrointestinal symptoms that are easily tolerated 2: Moderate: Gastrointestinal symptoms that interfere with normal activity 3: Severe:Gastrointestinal symptoms that prevent normal activity | | | | | | | | | | | | | |

†Gastrointestinal symptoms include nausea, vomiting, diarrhoea and/or abdominal pain.

* Medical attention = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 2** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## ADVERSE EVENTS

Record any adverse event (= any illness, sign, symptom) other than the local and general symptoms solicited on the previous pages, which may have started or any medical condition which may have worsened since the last study vaccination.

| **Illness/Sign/Symptom**<br>☑ if at vaccine injection site ↓ | **Max Intensity**<br>1/2/3 | **Start Date** | **End Date** | **Did you receive medical attention?*** | **Type of medical attention**<br>To be completed by the investigator |
|---|---|---|---|---|---|
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |
| ☐ | | | | ☐ No<br>☐ Yes | HO/ER/MD<br>\|_\|_\| |

**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).
* **Medical attention** = hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor)

**In case of hospitalization, please inform:**

.....

## MEDICATION

Record any medication taken since the last study vaccination.

| **Medication** | **Reason/Indication** | **Route**<br>To be completed by the investigator | **Dose and frequency** | **Start Date** | **End Date** |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010

# VISIT 3

| 113808 (Rota-075) | **DIARY CARD** Visit 3 | **Subject Number** \|__\|__\|__\|__\|__\|__\| To be completed by the investigator |
|---|---|---|

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |
| | | \|__\|__\|\|__\|__\|__\|\|__\|__\|__\|__\| day month year |

**Route:**

| | | | |
|---|---|---|---|
| ID | = Intradermal | PE | = Parenteral |
| IH | = Inhalation | PO | = Oral |
| IM | = Intramuscular | SC | = Subcutaneous |
| IN | = Intranasal | SL | = Sublingual |
| IV | = Intravenous | TD | = Transdermal |
| OTH | = Other | UNK | = Unknown |

| | | |
|---|---|---|
| GlaxoSmithKline 113808 (Rota-075) | **DIARY CARD**<br>**Visit 3** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | Route<br>To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
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## NOTES

| |
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| |

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010

# VISIT 4

| | | |
|---|---|---|
| 113808<br>(Rota-075) | **DIARY CARD**<br>**Visit 4** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

## CONCOMITANT VACCINATION

Record any vaccine administered since the last study vaccination.

| Vaccine Name | Route | Date of administration |
|---|---|---|
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |
| | | \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|<br>day month year |

**Route:**

ID = Intradermal
IH = Inhalation
IM = Intramuscular
IN = Intranasal
IV = Intravenous
OTH = Other
PE = Parenteral
PO = Oral
SC = Subcutaneous
SL = Sublingual
TD = Transdermal
UNK = Unknown

Diary Card template13.1 – August 06, 2010

| 113808 (Rota-075) | **DIARY CARD**<br>**Visit 4** | **Subject Number**<br>\|___\|___\|___\|___\|___\|___\|<br>To be completed by the investigator |
|---|---|---|

## MEDICATION

Record any medication taken since the last study vaccination.

| Medication | Reason/Indication | **Route**<br>To be completed by the investigator | Dose and frequency | Start Date | End Date |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

## NOTES

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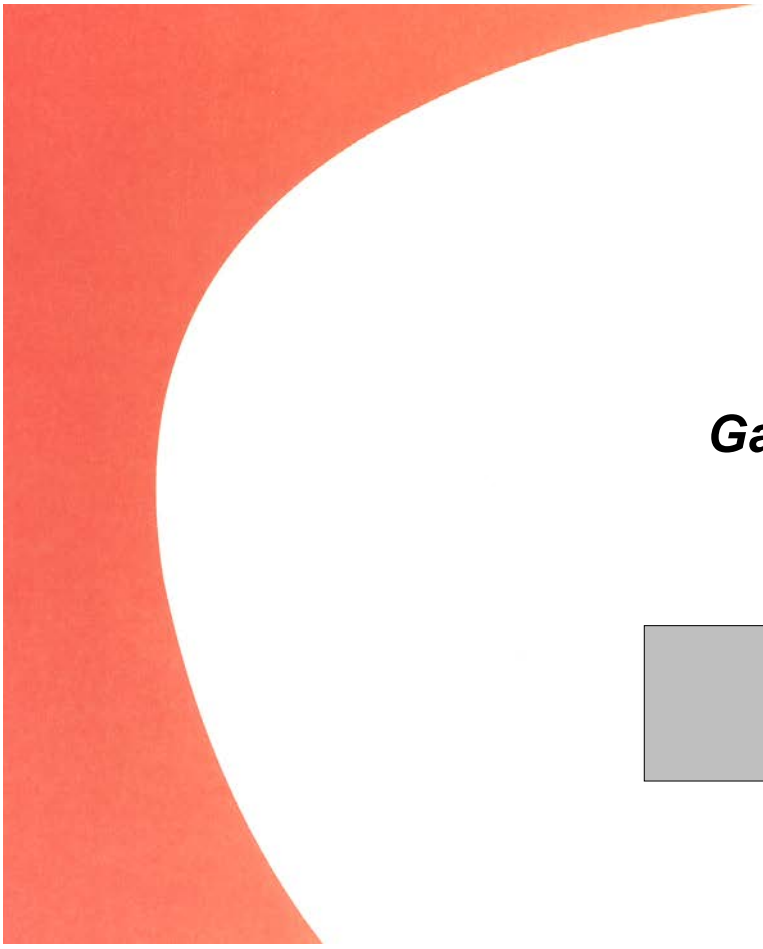
| |

**PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON NEXT VISIT**

Diary Card template13.1 – August 06, 2010



GlaxoSmithKline

# *Gastroenteritis Diary Card*

***Subject number***

|__|__|__|__|__|__|__|

To be completed by the Investigator

## *Protocol 113808 (Rota-075)*

***A phase III, double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine in healthy Chinese infants.***

Diary Card template13.1 – July 21, 2010

## For all Subjects who experience

## Gastroenteritis Episodes

CONFIDENTIAL

| | | |
|---|---|---|
| 113808<br>(Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms

Treatment?
☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| GlaxoSmithKline 113808 (Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |
|---|---|---|

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: _____

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** ☐ **Axillary** (*) ☐ Oral ☐ Rectal | |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | |
|---|---|---|
| GlaxoSmithKline 113808<br>(Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms GE symptoms

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: _________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | | |
|---|---|---|---|
| gsk GlaxoSmithKline | 113808<br>(Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms GE symptoms

Treatment? ☐ No
☐ Yes → ☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: ___________________________

Medical advice: ☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

| | | |
|---|---|---|
| 113808<br>(Rota-075) | **Gastroenteritis**<br>**DIARY CARD** | **Subject Number**<br>\|__\|__\|__\|__\|__\|__\|<br>To be completed by the investigator |

Please record any GE episodes occurring after vaccination and during visit intervals daily until end of the GE symptoms GE symptoms

Treatment?
☐ No
☐ Yes →
☐ Oral rehydration
☐ IV rehydration
☐ Oral and IV rehydration
☐ Other, please specify: __________________________

Medical advice:
☐ Medical doctor
☐ Emergency room
☐ Hospitalization

Date of medical advice: |__|__| |__|__|__| |__|__|__|__|

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

Stool collection date and time: |__|__| |__|__|__| |__|__|__|__| |__|__|:|__|__|
day month year hours min

| **Date**<br>day month year | **Number of looser than normal stools per day** | **Number of vomiting per day** | **Temperature (°C) → route:** | ☐ **Axillary** (*)<br>☐ Oral<br>☐ Rectal |
|---|---|---|---|---|
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |
| \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| | \|__\|__\| | \|__\|__\| | \|__\|__\|.\|__\| | ☐ not taken |

(*) **route: axillary is mandatory.**

Diary Card template13.1 – July 21, 2010

# List of Independent Ethics Committees /Institutional Review Boards

| Centre Number(s)* | Ethics Review Body | Location |
|---|---|---|
| [redacted] | [redacted] | [redacted]<br>Phone [redacted]<br>Email: [redacted] |

* GSK Biologicals assigned centre number

# Representative written information for patient and sample consent forms

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 01 (update with Version of Local ICF)**

**Date: 06 August 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease) and safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools

are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 2350 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she

is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit. |

Informed Consent Form for Efficacy subgroup

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| **Day** | **What will happen at this visit** |
|---|---|
| | Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.
- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that**

**any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, 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. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. Preliminary data from a large post-marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31-day period following the first dose. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose.
These observations are limited to the first dose and not seen following administration of the second dose. Parents/guardians are asked to contact the study doctor if they noticed any signs and symptoms indicative and/or consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever).

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

GSK has identified the presence of material from Porcine circovirus-1 (PCV-1), a virus to which people are commonly exposed, in its Human Rotavirus Vaccine. There is no evidence that PCV-1 can infect humans or is harmful to humans. Based on these considerations and the extensive safety database available, the benefit/risk profile of GSK Biologicals' HRV vaccine has not changed and remains favourable.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this

study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Efficacy subgroup Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 01, 15 pages, dated 06 August 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Efficacy subgroup Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 01 (update with Version of Local ICF)**

**Date: 06 August 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 600 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

Informed Consent Form- for Immunogenicity subgroup 1

**CONFIDENTIAL**

113808 (ROTA-075)

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 1

**CONFIDENTIAL**

113808 (ROTA-075)

**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 3 millilitres)<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination. |

| **Day** | **What will happen at this visit** |
|---|---|
| | Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit.<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination.<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the

next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, 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. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. Preliminary data from a large post-marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31-day period following the first dose. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose.

These observations are limited to the first dose and not seen following administration of the second dose. Parents/guardians are asked to contact the study doctor if they noticed any signs and symptoms indicative and/or consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever).

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

GSK has identified the presence of material from Porcine circovirus-1 (PCV-1), a virus to which people are commonly exposed, in its Human Rotavirus Vaccine. There is no evidence that PCV-1 can infect humans or is harmful to humans. Based on these considerations and the extensive safety database available, the benefit/risk profile of GSK Biologicals' HRV vaccine has not changed and remains favourable.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from**

**samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

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## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 01, 15 pages, dated 06 August 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

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I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 01 (update with Version of Local ICF)**

**Date: 06 August 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 300 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she did not receive any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.
- He/she does not or has not had any history of diphtheria, tetanus and pertussis disease.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she does not have a disease that affects his/her nervous system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (Visit 6 = concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 2

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 4.5 millilitres)<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after Dose 1 of OPV vaccine<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>DTPa vaccine given on left thigh<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days |

Informed Consent Form- for Immunogenicity subgroup 2

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| Day | What will happen at this visit |
|---|---|
| | (Days 0 – 7) after Dose 2 of OPV vaccine and Dose 1 of DTPa<br><br>Daily post-vaccination recording of solicited local adverse events within 8-days (Days 0 – 7) after Dose 1 of DTPa vaccine<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>Collection of blood sample (not more than 3 millilitres)<br><br>OPV vaccine given orally<br><br>DTPa vaccine given on left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br><br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 3 (Visit 4) | Return gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>DTPa vaccine injected on the left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and Visit 4)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 3 and Visit 4<br><br>Recording of any medical condition your child/ward has experienced between Visit 3 and Visit 4<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 4 (Visit 5) | Return gastroenteritis dairy cards given at previous visit |

Informed Consent Form- for Immunogenicity subgroup 2

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| Day | What will happen at this visit |
|---|---|
| | Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 4 and Visit 5)<br>Recording of any medication/vaccination your child/ward has received between Visit 4 and Visit 5<br>Recording of any medical condition your child/ward has experienced between Visit 4 and Visit 5<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age (Visit 6) | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 5 till your child/ward is one year of age [Visit 6])<br>Recording of any medication/vaccination your child/ward has received between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of any medical condition your child/ward has experienced between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of serious adverse events<br>Study Conclusion |

- DTPa vaccine is a vaccine against diphtheria, tetanus and pertussis [whooping cough]) and OPV vaccine is a vaccine against polio.

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.

- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.

  – body (axillary) temperature.

  – solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- You will receive diary cards to record information of your child/ward on the following after the first two doses of the OPV vaccine and the first dose of the DTPa vaccine

  – body (axillary) temperature.

  - solicited (expected) general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) for DTPa and OPV vaccine and solicited (expected) local symptoms (pain, swelling, redness) for DTPa vaccine occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

- Your child/ward will also receive his/her routine childhood vaccinations recommended in China.

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, 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. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. Preliminary data from a large post-

marketing epidemiological safety study in Mexico indicate a possible increased risk of intussusception in the 31-day period following the first dose. Spontaneous reports of intussusception have been received mostly within 7 days after the first dose.
These observations are limited to the first dose and not seen following administration of the second dose. Parents/guardians are asked to contact the study doctor if they noticed any signs and symptoms indicative and/or consistent with intussusception (severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever).

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

GSK has identified the presence of material from Porcine circovirus-1 (PCV-1), a virus to which people are commonly exposed, in its Human Rotavirus Vaccine. There is no evidence that PCV-1 can infect humans or is harmful to humans. Based on these considerations and the extensive safety database available, the benefit/risk profile of GSK Biologicals' HRV vaccine has not changed and remains favourable.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

The following side effects may occur when your child/ward receives DTPa and OPV vaccines:

Like all medicines, DTPa can cause side effects, although not everybody gets them. Side effects that may occur are the following:

The following side effects related to study procedures may occur: (this may occur with up to more than 1 in 10 doses): irritability, sleepiness, redness and swelling at the injection site, fever (≥ 38.0°C).

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses): loss of appetite, restlessness, abnormal crying, diarrhoea, vomiting, itching, pain at the injection site.

The following side effects are less likely: (these may occur with up to 1 in 100 doses): headache, cough, bronchitis, rash, hard lump at the injection site, fatigue, fever (≥39.1°C)

The following side effects are rare: (these may occur 1 in 1000 doses of the vaccine): hives

The following side effects are very rare: (these may occur 1 in 10,000 doses of the vaccine):

As with all injectable vaccines, there is an extremely small risk of severe allergic reactions. These can be recognised by:

- Itchy rash of the hands and feet
- Swelling of the eyes and face
- Difficulty in breathing or swallowing.

These reactions will usually occur before leaving the doctor's surgery. However, if your child/ward gets any of these symptoms you should contact a doctor urgently.

- Swollen glands in the neck, armpit or groin
- Bleeding or bruising more easily than normal
- Collapse or periods of unconsciousness, lack of awareness, seizures or fits (with or without fever) which usually occur within 2 to 3 days after vaccination
- Temporarily stopping breathing
- Swelling of the entire injected limb

Like all medicines, OPV can cause side effects, although not everybody gets them. Side effects that may occur are the following:

Generally there are no adverse reactions after oral intake of OPV vaccine. The following side effects may occur in some subjects: fever, nausea, vomit, diarrhoea, and rashes. No special intervention is indicated generally, symptomatic treatment may be administered if necessary.

Vaccine associated paralytic poliomyelitis (VAPP) may be caused by inoculation of live attenuated poliomyelitis, and there is no exact statistical data domestically. VAPP incidence rates are 2-4 in one million, according to official statistical report by World Health Organization.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgments made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.

- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

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## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 01, 17 pages, dated 06 August 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

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I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian _____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent _____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness _____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**STUDY INFORMATION LETTER**

**FOR SUBJECT'S PARENTS/GUARDIANS WHO SIGNED THE MODEL ICF VERSION 01 DATED: 06-AUG-2010**

**(For all the subjects in this study: Subjects in Efficacy subgroup, Immunogenicity subgroup 1 and Immunogenicity subgroup 2)**

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Information Letter version 1 dated 13 October 2010 (update with Version and date of Local information letter)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## Purpose of this document

By means of this document we want to thank you for your child's/ward's participation in this study. Through this information letter we want to inform you about the few updates which were made to the Rota-075 Informed Consent Form Version 01 dated 06 August 2010, a copy of which was handed over to you during the consent process. **Please take time to read the following information and ask us if you have any questions.** The following updates were done to the section titled "**What side effects or risks can you expect for your child/ward in the study?**"

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However, preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*, with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

Material from Porcine circovirus type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 02 (update with Version of Local ICF)**

**Date: 02 September 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease) and safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools

are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 2350 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she

is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form for Efficacy subgroup

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit. |

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| Day | What will happen at this visit |
|---|---|
| | Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.
- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that**

**any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*, with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the

non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

Material from *Porcine circovirus* type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this

study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Efficacy subgroup Subject ID_____

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113808 (ROTA-075)

## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 02, 15 pages, dated 02 September 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Efficacy subgroup Subject ID_____

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I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 02 (update with Version of Local ICF)**

**Date: 02 September 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 600 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

Informed Consent Form- for Immunogenicity subgroup 1

**CONFIDENTIAL**

113808 (ROTA-075)

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 1

**CONFIDENTIAL**

113808 (ROTA-075)

**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 3 millilitres)<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after first dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after second dose of HRV vaccine/placebo<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination. |

Informed Consent Form- for Immunogenicity subgroup 1

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| Day | What will happen at this visit |
|---|---|
| | Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit.<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination.<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and till your child/ward is one year of age)<br>Recording of any medication/vaccination your child/ward has received between Visit 3 till your child/ward is one year of age<br>Recording of any medical condition your child/ward has experienced between Visit 3 till your child/ward is one year of age<br>Recording of serious adverse events<br>Study Conclusion |

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.
  - body (axillary) temperature.
  - solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the

next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*,

with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

Material from Porcine Circovirus type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from**

**samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgements made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.
- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 1 Subject ID_____

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## Consent statement

I,

_____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 02, 15 pages, dated 02 September 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

*<Note: Not applicable if study doctor is healthcare doctor.>*

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

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I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

**Instructions for Local ICF development**

The author of the Model ICF should indicate in **BOLD RED TEXT** (Normal style) any items for which country-specific or site-specific information is to be added in the Local ICF. The CMD should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and template.

When developing a Local ICF, all changes to the content which affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK preferred wording and should be retained, any changes to this text must be communicated to the central team or local representative, as appropriate.

**Note:** In the final Local ICF all text should be in the same format i.e. any bold text should be reformatted to match the rest of the contents.

Refer to INS-WWD-1040, SOP-WWD-1040 and GUI-WWD-0013 for more information.

**(Delete the instructions above from the Final Local ICF).**

# INFORMED CONSENT FORM

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Model ICF Version Number: 02 (update with Version of Local ICF)**

**Date: 02 September 2010 (update with Date of Local ICF)**

**Company Name: GlaxoSmithKline (GSK) Biologicals S.A.**

**Subject Identification: _____**

**Insert subject ID here**

*This document should be presented to the subject's parent / guardian in full; no pages or sections should be omitted. The document contents should be explained verbally to the subject's parent / guardian.*

## What is consent?

Consent means agreeing to take part in this research study. You can decide if you want your child/ward to take part in the study or not. Please take time to read the following information and ask us if you have any questions. You can talk in confidence with family, friends and your family doctor to help you make a decision. You must sign the pages at the end of this form if you decide to let your child/ward to join the study. You will receive a copy of this form for your record.

## Why is this study being done?

The purpose of this research study is to test the efficacy (how effective the vaccine is in preventing a disease), antibody levels (proteins the body makes to protect it against a specific disease), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

A virus is a micro-organism smaller than bacteria that invades living cells and causes diseases. The most common cause of diarrhoeal illness (which is 3 or more looser than normal stools within 24 hours) in infants and young children is a virus called "rotavirus". Virtually, all children suffer from rotavirus diarrhoea, and most often children between 6 and 24 months of age are affected.

Symptoms of rotavirus disease (or gastroenteritis) mainly include diarrhoea and vomiting. Other symptoms such as fever and abdominal pain may also occur. The diarrhoeal stools are loose and watery with up to ten stools per day. The symptoms last from 3 to 9 days. Diarrhoea can cause loss of water and important nutrients resulting in dehydration that may require hospital treatment. Gastroenteritis due to rotavirus is a common cause of hospitalisation of young children in developed countries and is the leading cause of death in poorer countries. It is estimated that rotavirus is accountable for more than 527, 000 (475, 000 – 580, 000) deaths per year worldwide with majority of the deaths occurring in developing countries like Asia and Africa. In China, rotavirus is a leading cause of severe gastroenteritis among children less than 5 years of age and is an economic burden for the parents. Approximately 27, 000 rotavirus-associated deaths occurring each year and 32-50% of hospitalized diarrhoea is associated with rotavirus infection in China.

Since there is no specific treatment available for rotavirus, vaccination is the best way to prevent rotavirus gastroenteritis. Vaccines work by stimulating the body to produce antibodies (proteins the body makes to protect it against a specific disease) against diseases. GSK Biologicals, a pharmaceutical company, has developed a HRV vaccine. The study will assess efficacy (how effective the vaccine is in preventing a disease) of the HRV vaccine relative to the placebo (a product that looks like the vaccine but has no activity/effect). This study will also investigate the immune response (ability of your child's/ward's body to develop antibodies that fight infection after vaccination), safety (in terms of occurrence of any serious adverse events) and reactogenicity (any side effects) of the HRV vaccine relative to a placebo when given along with the routine Expanded Program on Immunisation (EPI) childhood vaccines in China.

GSK Biologicals' HRV vaccine has already undergone efficacy, immunogenicity and safety studies in many countries, including Europe and the US, and the HRV vaccine has been well-tolerated, immunogenic and efficacious in preventing rotavirus gastroenteritis in infants.To date, the HRV vaccine has been approved for use in infants in more than hundred countries.

## How many subjects are in the study?

Approximately 3250 infants (male and female) will take part in this study.

## What does this study involve?

For the 3250 subjects taking part in the study, there will be two groups (HRV and placebo), comprising of 1625 subjects in each group. In addition, the study will also have three subgroups. After your child/ward has been allotted to a group (HRV or placebo), he/she may be assigned into one of the subgroups. This ICF involves procedures pertaining to one of the subgroups which comprises of approximately 300 subjects.

A process called randomisation will be used to assign your child/ward to any one of the two study groups. Randomisation means that the participants are put into a group by chance. A computer will put subjects into groups by chance. Neither you nor the study doctor can choose a group. The study doctor and the people who take part will not know which group will be receiving which vaccine.

You will be asked to bring your child/ward to see the study doctor or his delegate, who will ask questions about your child's/ward's health and examine him/her to see if he/she is qualified for the study. Your child/ward can only take part in this study if all of the following apply to him/her:

- He/she is a healthy child, aged between 6 and 16 weeks at the time of the first vaccine dose.
- He/she is born after a gestation period of 36 to 42 weeks inclusive.
- You give written consent to permit his/her participation in the study.
- He/she did not receive any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis.
- He/she does not or has not had any history of diphtheria, tetanus and pertussis disease.
- He/she does not or did not take medications that suppress reactions of the immune system and does not have a disease related to the immune system.
- He/she does not have a disease that affects his/her nervous system.
- He/she did not receive an experimental medication/vaccine within 30 days before the beginning of this study, and will not receive such a product/vaccine for the entire duration of the study.

The expected duration of your child's/ward's participation in this study is approximately till your child/ward attains one year of age (Visit 6 = concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date at the discretion of the study doctor.

If you let your child/ward take part in this study it is important that you follow all applicable study related procedures as requested.

Informed Consent Form- for Immunogenicity subgroup 2

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**The table below shows what will happen at each study visit:**

| Day | What will happen at this visit |
|---|---|
| Day 0 (Visit 1) | Consent process<br>Recording of previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Medical history<br>Physical examination<br>Recording of body temperature<br>Recording of gestational age<br>Recording height, weight<br>Collection of blood sample (not more than 4.5 millilitres)<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>Collection of stool samples in case the child/ward develops gastroenteritis<br>Recording of any medication/vaccination your child/ward has received prior to Visit 1<br>Recording of any medical condition your child/ward has experienced prior to Visit 1<br>Daily post-vaccination recording of solicited general adverse events within 8-days (Days 0 – 7) after Dose 1 of OPV vaccine<br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br>Recording of serious adverse events<br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 1 (Visit 2) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br>Physical examination<br>Recording of body temperature<br>HRV vaccine or placebo given orally<br>OPV vaccine given orally<br>DTPa vaccine given on left thigh<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 1 and Visit 2)<br>Recording of any medication/vaccination your child/ward has received between Visit 1 and Visit 2<br>Recording of any medical condition your child/ward has experienced between Visit 1 and Visit 2<br>Daily post-vaccination recording of solicited general adverse events within 8-days |

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| Day | What will happen at this visit |
|---|---|
| | (Days 0 – 7) after Dose 2 of OPV vaccine and Dose 1 of DTPa<br><br>Daily post-vaccination recording of solicited local adverse events within 8-days (Days 0 – 7) after Dose 1 of DTPa vaccine<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Diary card will be given to record symptoms that your child/ward may experience up to the next visit<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 2 (Visit 3) | Return completed diary card and gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>Collection of blood sample (not more than 3 millilitres)<br><br>OPV vaccine given orally<br><br>DTPa vaccine given on left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 2 and Visit 3)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 2 and Visit 3<br><br>Recording of any medical condition your child/ward has experienced between Visit 2 and Visit 3<br><br>Recording of non-serious adverse events within 31 days (Day 0 – 30) post-vaccination<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 3 (Visit 4) | Return gastroenteritis dairy cards given at previous visit<br><br>Record of any previous vaccination against diphtheria, tetanus, pertussis and poliomyelitis<br><br>DTPa vaccine injected on the left thigh<br><br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 3 and Visit 4)<br><br>Recording of any medication/vaccination your child/ward has received between Visit 3 and Visit 4<br><br>Recording of any medical condition your child/ward has experienced between Visit 3 and Visit 4<br><br>Recording of serious adverse events<br><br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| Month 4 (Visit 5) | Return gastroenteritis dairy cards given at previous visit |

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| Day | What will happen at this visit |
|---|---|
| | Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 4 and Visit 5)<br>Recording of any medication/vaccination your child/ward has received between Visit 4 and Visit 5<br>Recording of any medical condition your child/ward has experienced between Visit 4 and Visit 5<br>Recording of serious adverse events<br>Gastroenteritis diary cards will be given to record gastroenteritis (three or more looser than normal stool within a day with or without vomiting) up to the next visit |
| When your child/ward is one year of age (Visit 6) | Return completed gastroenteritis dairy cards given at previous visit<br>Collection of blood sample (not more than 3 millilitres)<br>Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 5 till your child/ward is one year of age [Visit 6])<br>Recording of any medication/vaccination your child/ward has received between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of any medical condition your child/ward has experienced between Visit 5 till your child/ward is one year of age (Visit 6)<br>Recording of serious adverse events<br>Study Conclusion |

- DTPa vaccine is a vaccine against diphtheria, tetanus and pertussis [whooping cough]) and OPV vaccine is a vaccine against polio.

- After each vaccination, your child/ward will be kept under observation for 30 minutes to check for any immediate vaccine reactions.

- You will receive diary cards to record information of your child/ward on the following after each dose of HRV vaccine / placebo.

  – body (axillary) temperature.

  – solicited (expected) general symptoms (such as fever, fussiness/irritability, diarrhoea, vomiting, loss of appetite and cough/runny nose) occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- You will receive diary cards to record information of your child/ward on the following after the first two doses of the OPV vaccine and the first dose of the DTPa vaccine

  – body (axillary) temperature.

  - solicited (expected) general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite and gastrointestinal symptoms) for DTPa and OPV vaccine and solicited (expected) local symptoms (pain, swelling, redness) for DTPa vaccine occurring for the next 8 days of vaccination (i.e. on the day of vaccination and during the next 7 days), on any medications/vaccinations.

- unsolicited (unexpected) adverse events occurring within 31 days of vaccination (i.e. on the day of vaccination and during the next 30 days).

- You should contact the study doctor or his staff immediately should your child/ward manifest any signs or symptoms that you perceive as serious.

- You will receive a gastroenteritis dairy card to record information of your child/ward on any gastroenteritis episodes occurring between the study visits. The gastroenteritis diary card should be completed by you daily until end of the gastroenteritis symptoms (defined as three or more looser than normal stool within a day with or without vomiting).

- You should also collect a stool sample from your child/ward every time your child/ward experiences a gastroenteritis (diarrhoea- which is 3 or more loose than normal stool within 24 hours) episode. Stool sample should be collected as soon as possible after gastroenteritis symptoms begin. A second stool sample should be collected if the first sample is insufficient. If there are 5 or more diarrhoea free days between the two occurrences of GE, it should be considered as a separate episode and a stool sample should be taken again. Samples should be transferred rapidly to the study doctor's laboratory or study doctor's site (within 0 to 3 days).

- Your child/ward will also receive his/her routine childhood vaccinations recommended in China.

If you wish to stop the participation of your child/ward or if you have not followed the instructions listed above, it is important that you notify the study doctor or study staff.

## What will happen to samples taken in this study?

**Samples will not be labelled with information that directly identifies your child/ward but will be coded with an identification number.**

**Collected samples may be transferred to GSK Biologicals and other laboratories working for GSK Biologicals.**

**By agreeing to let your child/ward take part in this study you will be allowing GSK Biologicals to use your child's/ward's samples for the following purposes:**

- Testing the presence and characteristics of rotavirus in the stool of your child/ward to evaluate efficacy of the vaccine.

- To measure the immune response (e.g. amount of antibodies) to the vaccines your child/ward received during the study.

- **To assure that the tests used in this study remain of high quality and can be repeated or compared with the results from other studies.**

- **To assess, improve or develop tests related to the disease or the vaccine under study that will allow more reliable measurement of the response to the vaccine. This excludes testing related to your child's/ward's genes' hereditary characteristics and HIV.**

Collected samples will be stored for up to 15 years.

**In addition, if you agree, your child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or the vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking your child/ward to the sample is destroyed). Testing on your child's/ward's genes' hereditary characteristics or testing for HIV will not be done. You will be asked if you agree to this on the final consent page. This testing is optional and does not affect your child's/ward's participation in the study.**

## What side effects or risks can you expect for your child/ward in the study?

Over 131, 000 infants have been enrolled in studies with GSK Biologicals' HRV vaccine. During these studies, over 53, 000 infants have received at least one dose of the vaccine.

As with any vaccine, unexpected illnesses (called serious adverse experiences), including allergic reactions to the vaccine, (itchy skin rash, shortness of breath and swelling of the face or tongue) may occur. Medical equipment necessary to treat any serious reactions to the study vaccine will be available at the site.

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses of HRV vaccine): diarrhoea.

The following side effects are less likely: (these may occur with up to 1 in 100 doses of HRV vaccine): flatulence (gas), abdominal pain and dermatitis.

The following side effects are rare: (these may occur 1 in 1000 doses of HRV vaccine): blood in stools has been observed.

There may be other side effects that are not known now.

Your child/ward should not receive the HRV vaccine of this study if he/she has a chronic disease or congenital (by birth) malformation of the digestive system (intestine) nor if he/she has developed an allergic reaction to an ingredient of the vaccine.

In the past, a different rotavirus vaccine called RotaShield™ may have caused a very rare condition called intussusception. Intussusception is a blockage or twisting of part of the intestine that requires immediate attention by a doctor. The signs may include severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever. Results of a large safety trial conducted in Latin America and Finland with 63,225 infants

showed that HRV vaccine does not increase the risk of intussusception as compared to placebo. However preliminary data from a large post-marketing safety study indicate a possible increased risk of intussusception in the 31days after the first dose of *Rotarix*, with most cases reported within 7 days after the first dose. These observations are limited to the first dose and not seen following administration of the second dose. After your child/ward has received *Rotarix*, contact your doctor/health care professional right away if your child/ward experiences severe stomach pain, persistent vomiting, blood in stools, a swollen belly and/or high fever.

There have been few cases observed earlier where the HRV vaccine strain has shown to be transmitted from vaccinated infants to non-vaccinated subjects. However, none of the non-vaccinated subjects reported any gastrointestinal symptoms (diarrhoea, vomiting or fever) and were in good health.

Material from Porcine Circovirus type 1 (PCV-1), a virus commonly detected in animals, has been found in *Rotarix* vaccine. PCV-1 is not known to cause disease in animals and is not known to infect or cause disease in humans. There is no evidence that the presence of PCV-1 poses a safety risk.

If your child/ward experiences fever, diarrhoea or vomiting at the planned time for vaccination, he/she may be vaccinated at a later date or withdrawn at the discretion of the study doctor.

Your child/ward will receive the locally recommended routine childhood vaccinations during the study. These vaccines may cause side effects including pain and swelling at the injection site, high fever, crying or tiredness (fatigue). Further details on the side effects of routine childhood vaccines will be explained by the doctors upon request.

The following side effects may occur when your child/ward receives DTPa and OPV vaccines:

Like all medicines, DTPa can cause side effects, although not everybody gets them. Side effects that may occur are the following:

The following side effects related to study procedures may occur: (this may occur with up to more than 1 in 10 doses): irritability, sleepiness, redness and swelling at the injection site, fever (≥ 38.0°C).

The following side effects related to study procedures may occur: (this may occur with up to 1 in 10 doses): loss of appetite, restlessness, abnormal crying, diarrhoea, vomiting, itching, pain at the injection site.

The following side effects are less likely: (these may occur with up to 1 in 100 doses): headache, cough, bronchitis, rash, hard lump at the injection site, fatigue, fever (≥39.1°C)

The following side effects are rare: (these may occur 1 in 1000 doses of the vaccine): hives

The following side effects are very rare: (these may occur 1 in 10,000 doses of the vaccine):

As with all injectable vaccines, there is an extremely small risk of severe allergic reactions. These can be recognised by:

- Itchy rash of the hands and feet
- Swelling of the eyes and face
- Difficulty in breathing or swallowing.

These reactions will usually occur before leaving the doctor's surgery. However, if your child/ward gets any of these symptoms you should contact a doctor urgently.

- Swollen glands in the neck, armpit or groin
- Bleeding or bruising more easily than normal
- Collapse or periods of unconsciousness, lack of awareness, seizures or fits (with or without fever) which usually occur within 2 to 3 days after vaccination
- Temporarily stopping breathing
- Swelling of the entire injected limb

Like all medicines, OPV can cause side effects, although not everybody gets them. Side effects that may occur are the following:

Generally there are no adverse reactions after oral intake of OPV vaccine. The following side effects may occur in some subjects: fever, nausea, vomit, diarrhoea, and rashes. No special intervention is indicated generally, symptomatic treatment may be administered if necessary.

Vaccine associated paralytic poliomyelitis (VAPP) may be caused by inoculation of live attenuated poliomyelitis, and there is no exact statistical data domestically. VAPP incidence rates are 2-4 in one million, according to official statistical report by World Health Organization.

During the study, about half a teaspoon of blood will be collected from your child/ward at each pre-defined visit.

Your child/ward may experience pain and bruising of the skin at the needle site where blood is drawn and momentary discomfort but this involves no harmful effect to your child's/ward's health. In rare cases, an infection may develop at the site where blood is drawn or the vaccination is given. This is very unlikely, since your child's/ward's skin will be swabbed with alcohol before the injection and only sterile equipment will be used. 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).

## What benefits can you expect for your child/ward in the study?

Infants who receive the HRV vaccine may have the benefit of being protected against rotavirus disease.

By letting your child/ward participate in this study, your child/ward will help in evaluation of this vaccine and ultimately make it available for infants to protect them from RV diseases. In addition, your child/ward will undergo a physical examination at each study visit. In case the study doctor discovers any medical condition, your child/ward will be referred to the local healthcare system.

## Are there other products or treatment?

The following alternative treatments and vaccines may be available to you:

- Lanzhou vaccine against rotavirus infection is marketed in China, hence, an alternative would be to buy this vaccine outside the study and not be a part of this study.
- Disease caused by rotavirus is treated with oral rehydration solutions (special fluids given by mouth to prevent or treat excessive fluid loss) or if necessary, intravenous (IV) fluid replacement. This is to prevent dehydration (excessive loss of water from the body). There is no treatment to shorten the illness or to reduce vomiting or diarrhoea.

Talk with your doctor about the risks and benefits of the alternatives that may be available to your child/ward, before you decide to let your child/ward take part in this study.

**This section should be completed locally using the most current information regarding the alternatives which are available in the country.**

## Does your child/ward have to stay in the study?

Your child's/ward's participation in this study is voluntary. You may refuse to let your child/ward to take part in this study, or once in the study you may decide to discontinue your child's/ward's participation at any time. You must inform your study doctor if you decide to do this. Your decision not to let your child/ward to take part in the study or to stop participating in the study will not affect your child/ward current or future medical care, or any benefits to which your child/ward may otherwise be entitled.

We may stop your child's/ward's participation if:

- You do not follow instructions for your child's/ward's treatment or follow up visits.
- The results of certain tests show that this study is not appropriate for your child/ward.

GSK (the study sponsor) may choose to stop the study or the study doctor may choose to stop taking part in the study at any time. We will give you the reason at that time.

We will share with you any new information that might affect your choice to let your child/ward stay in the study as soon as possible.

**Check local regulations and seek local legal advice for the use of data after subject withdrawal. If changes are necessary the wording should be adapted and the central team informed, so that the impact for database collection can be taken into account.**

**If you decide for your child/ward to leave the study, all data collected before your child/ward left the study will still be used for the study. This includes any data from samples taken before your child/ward left the study. Any relevant safety information reported after your child/ward leaves the study will also be collected.**

**After completion of this study you may be asked if you are interested to allow your child/ward take part in other related studies and if not the reason will be recorded.**

## If your child/ward is injured in the study what compensation will be available?

If your child/ward is injured by a vaccine or a clinical procedure that your child/ward would not have been given outside this study, your child/ward will be compensated. The study doctor can provide you with information about the compensation guidelines for this kind of injury.

If your child's health deteriorates significantly because of his/her taking part in this study, your child will be paid compensation. How much to pay is worked out by looking at court judgments made at the time your child was injured, to see what people with similar injuries were awarded.

## Who should you contact if you have questions?

***Note: This section may be completed at Country Level (see red bold text)***

You may ask questions about the study. If you have any questions about the subject's rights and the research study itself or if you believe your child/ward has sustained a study-related injury, please contact:

Person to contact for any questions: **name, address, number**

Person to contact about your child's/ward's rights: **name, address, number**

Person to contact in case of injury: **name, address, number**

## Who will have access to your child's/ward's personal information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

If you decide to let your child/ward take part in the study, you allow us to use information about your child/ward and share it with GSK and others. This permission continues until the study is over, and does not end at a particular time.

Personal and medical information about your child/ward will be collected and kept confidential. It will be kept in a secured file. At any time, you may ask to see your child's/ward's personal information (such as name and address) and correct it if necessary.

Your child's/ward's study information will be used in two ways.

*Study management*

Information collected about your child/ward in the study will be checked by GSK and others (like the ethics board or government officials who approve new drugs) to make sure the study is being run properly. They will keep all information confidential.

*Study findings*

Medical information about your child/ward will be combined with information about other subjects in the study. This study information will be used to learn about the study vaccine. The study site will transfer some of the information it collects to GSK, in a coded form that will not include your child's/ward's name, initials, address, or other direct identifiers.

During the study, we may find new medical information about your child/ward. We will share this with the study doctor if it is important to your child's/ward's health. The study doctor will share it with you or your doctor. We may advise you to get other tests done for your child/ward, to check this new information.

Study information about your child/ward that is not helpful to your child's/ward's health care (such as which vaccine your child/ward is receiving or certain test results) will not be given to you or others (unless it is required by a government agency or other legal authority) during the study. This means that no one (not you, your family, your doctor, your insurance company, or your employer) will have access to this information. After the study is completed, you will be given access to any medical information about your child/ward.

## What will GSK do with the study information?

**If changes are made to this text the locals need to check with the local legal team that this is aligned with local procedures.**

The coded information collected by the study doctor will be sent to GSK, who may:

- Keep it and analyse it by computer to find out what this study is telling us.
- Share it with agencies that approve new vaccines, or with groups that check that research is done properly.

- Write up the study results for medical journals (this will not include any information that directly identifies your child/ward).
- Share it with other companies or universities to better understand the disease / or develop this vaccine. If the information is sent to another country, GSK will apply the same level of protection to your child's/ward's information, to the extent permitted by local law.
- Use it to plan new studies, other types of research or other medical purposes.

Information regarding the study and coded results will be publicly available on the internet. Information from this study may also be combined with the data from other studies in future.

## What payments will be made for the study?

**These sections should be completed locally.**

You will not be paid for your child's/ward's participation in this study.

## Will there be any cost/expenses in the study?

There is no cost for your child's/ward's participation in the study and all the study tests and procedures will be performed free of cost.

## How is GSK involved?

The study doctor and the institution are paid to conduct this research study by GSK. The vaccine is being developed for commercial purposes. GSK may use the results of this study to get patents / publications, or to sell the vaccine in the future or make profits. There is no plan to contact any participant now or in future about such commercial benefits.

GSK owns the information and materials given to you and your child/ward in the study. These should be kept private. You can discuss this information in confidence with your family doctor or friends and family to decide about letting your child/ward to take part in this study and also about your child's/ward's healthcare.

You will also receive a card that contains information about the study which can be used in the event of a medical emergency. You should keep this card with you at all times, and if your child/ward needs emergency medical treatment during the course of this study you should present this card to the medical staff treating your child/ward. If needed, the information on this card can be used by the medical staff to contact your study site and a request can be made about which study treatments your child/ward is receiving.

After considering all the information in this informed consent form you will be asked if you agree to let your child/ward take part in the study on the next page.

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

## Consent statement

I, _____

the parent / guardian of (Printed name of Subject's parent/guardian)

_____

Subject's name

- confirm that I have read the written information (or have had the information read to me) for study 113808 (ROTA-075), Version 02, 17 pages, dated 02 September 2010, **(update Version, page number and date locally)**, and the study procedures have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my child/ward to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my child/ward to take part in this study.

*Tick as appropriate (this decision will not affect your child's/ward's ability to enter the study):*

I agree that my healthcare doctor will be notified of my child's/ward's participation in this study.

<*Note: Not applicable if study doctor is healthcare doctor.*>

☐ **Yes** ☐ **No**

***Tick as appropriate***

**I agree that my child's/ward's biological samples may be used by GSK Biologicals for further research that is NOT RELATED to the disease or vaccine under study. This testing will be done on anonymised samples (meaning that any identification linking my child/ward to the sample is destroyed). Testing on my child/ward genes' hereditary characteristics or testing for HIV will not be done. I understand that if I select "No", it will not affect my child's/ward's participation in the study.**

☐ **Yes** ☐ **No**

Informed Consent Form for Immunogenicity subgroup 2 Subject ID_____

**CONFIDENTIAL**
113808 (ROTA-075)

I agree to let my child/ward take part in this study.

Name of Subject _____

Signature of subject's parent/guardian

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I have conducted the consent process according to applicable regulations.

Printed Name of Person conducting Consent _____

Signature of Person conducting consent

_____ Date: _____ dd/ mmm/ yyyy

I confirm that I am independent of the study, that I attended the informed consent process and that I have read the written information for the study.

*Printed name of Witness _____

Signature of Witness

_____ Date: _____ dd/ mmm/ yyyy

*Witness is only required if the subject's parent/guardian is unable to read.

Informed Consent Form Addendum

**CONFIDENTIAL**

Study Identification 113808 (ROTA-075)

**ADDENDUM 01 to the Informed Consent Form for the Subjects' Parents/ Legally Acceptable Representatives (LARs)**

**Study Identification:** 113808 (ROTA-075)

**Study Title:** Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) (444563), in healthy infants.

**Version and date: Version 1–05 August 2011**

**Company Name: GlaxoSmithKline Biologicals S.A.**

**Subject Identification: _____**

*This document should be presented to the subject's LAR in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the subject's LAR.*

## Purpose of this document

This document is an addendum to the Informed Consent Form that you had signed at the start of the 113808 (ROTA-075) study.

As explained to you in the original informed consent form, the purpose of this study is to evaluate the efficacy, immune response and safety of GSK Biologicals' of the human rotavirus (HRV) vaccine in Chinese infants aged 6 to 16 weeks at the time of first vaccination to support the vaccine registration in China.

The original ICF asked you if you would allow your child/ward to be part of this study till he/she is one year of age. However, during the study period lower number of rotavirus gastroenteritis cases were observed than anticipated. Therefore, in order to meet the primary objective of this study, the study participants are to be followed up till April 2012. If you agree to allow your child/ward to participate in this study extension, you will be asked to come to the study site for an additional visit (Visit 7).

Your consent is voluntary. Refusal will involve no penalty or loss of benefits or attention that your child is otherwise entitled to receive from your healthcare provider.

You should not sign this addendum unless you have received satisfactory answers to all of your questions. You will receive a signed copy of this addendum for your records.

Please find below the updated section entitled under the section "What does this study involve?" New text is shown in ***bold italics*** below:

The expected duration of your child's/ward's participation in this study ***will not exceed a maximum of 21 months*** (concluding visit to assess the health of your child/ward). The study nurse will review all the study procedures with you in detail.

Informed Consent Form Addendum

**CONFIDENTIAL**

Study Identification 113808 (ROTA-075)

| | |
|---|---|
| ***Visit 6*** | ***Addendum to be signed by the child/ward's parents or guardians*** |
| ***After visit 6 for subjects who have already completed Visit 6*** | ***Addendum to be signed by the child/ward's parents or guardians***<br>***Retrospective recording of intercurrent medical condition***<br>***Retrospective recording concomitant medication/vaccination***<br>***Retrospective follow-up on GE episodes***<br>***Retrospective recording of SAEs*** |
| ***Visit 7 (April 2012)***<br><br>***(For all subjects participating in the extended follow-up period)*** | ***Addendum to be signed by the child/ward's parents or guardians***<br>***Return completed gastroenteritis dairy cards given at previous visit***<br>***Collection of stool samples in case the child/ward develops gastroenteritis (between Visit 6 and Visit 7)***<br>***Recording of any medication/vaccination your child/ward has received between Visit 6 till Visit 7***<br>***Recording of any medical condition your child/ward has experienced between Visit 6 till Visit 7***<br>***Recording of serious adverse events***<br>***Study Conclusion*** |

Informed Consent Form Addendum Subject ID: _____

**CONFIDENTIAL**
Study Identification 113808 (ROTA-075)

## Consent statement

I,

_____
(Printed name of subject's parent/guardian)

the parent/ guardian of _____
Subject's name

- confirm that I have read the written information (or have had the information read to me) in the Addendum 01 Version 1-05 August 2011 to the Model ICF Version 1-06 August 2010 or Model ICF Version 2- 02 September 2010 (you may have received either one of the versions), for study 113808 (ROTA-075) and the changes have been explained to me by study staff during the consent process for this study.
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided.
- understand that I grant access to data about my son /daughter to authorised persons described in the information sheet.
- have been given time and opportunity to consider allowing my son /daughter to continue participating in the study.

I hereby agree to let my child continue to participate in this study.

| | | | |
|---|---|---|---|
| Printed name of subject's parent/guardian | _____ | Date: | |
| Signature of subject's parent/guardian | _____ | Date: | _____ day/ month/ year |
| Printed name of Witness (If needed) | _____ | | |
| *Signature of Witness | _____ | Date: | _____ day/ month/ year |
| Printed Name of Person explaining the *addendum* | _____ | | |
| Signature of Person explaining the *addendum* | _____ | Date: | _____ day/ month/ year |

*** Signature of witness is only required for those subject's whose parents/guardians are unable to sign their own name.**

# List of investigators and other important participants in the study, contact information and number and distribution of subjects

| Investigator's name | Sub-investigators | Centre number* | Investigational site | Location | Phone number Fax number | Number of Subjects | % of Subjects |
|---|---|---|---|---|---|---|---|
| Dr. [redacted] | [redacted] | [redacted] | [redacted] | [redacted] China | Phone: [redacted] Fax: [redacted] E-mail: [redacted] | 923 | 27.6% |
| Dr. [redacted] | [redacted] | [redacted] | [redacted] | [redacted] China | Phone: [redacted] Fax: [redacted] E-mail: [redacted] | 904 | 27.0% |

| Investigator's name | Sub-investigators | Centre number* | Investigational site | Location | Phone number<br>Fax number | Number of Subjects | % of Subjects |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Dr. | | | | China | Phone:<br>Fax:<br>E-mail: | 1,201 | 35.9% |

| Investigator's name | Sub-investigators | Centre number* | Investigational site | Location | Phone number Fax number | Number of Subjects | % of Subjects |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| Dr. [redacted] | [redacted] | [redacted] | [redacted] | [redacted] China | Phone: [redacted] Fax: [redacted] E-mail: [redacted] | 312 | 9.3% |

* GSK Biologicals' assigned centre number

# Investigator CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

*This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*

# Signature of principal or coordinating investigator

## GlaxoSmithKline Biologicals
## Vaccine Value and Health Science
## Investigator Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report Amendment 1 including appendices

STUDY TITLE: Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants

Study: 113808 (ROTA-075) 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: Dr [redacted]

Affiliation /investigational centre: [redacted]

Signature of Investigator: _____

Date: _____

For internal use only

- ----------Checksum----------!Ver.!Created On - -
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# GlaxoSmithKline Biologicals
# Vaccine Value and Health Science
# Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report Amendment 1 including appendices

STUDY TITLE: Efficacy, immunogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' oral live attenuated liquid human rotavirus (HRV) vaccine (444563), in healthy infants

Study: 113808 (ROTA-075) Development Phase: III

*I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.*

Name of Sponsor Signatory: [redacted]

Title of Sponsor Signatory: Director, Lead Clinical Development,
DTP Combination Vaccines and Rotavirus Vaccines, Late Clinical Development
GlaxoSmithKline Biologicals

Signature: _____

Date: _____

For internal use only

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## Listings of patients receiving test drug(s) /investigational product(s) from specific batches, where more than one batch was used

Not applicable.

# Randomisation list

## Randomization List

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
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| | 1 | | | 21 | | | 41 | | | 61 | | | 81 | | | 101 | | | 121 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |
| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
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| [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| 141 | | 161 | | 181 | | 201 | | 221 | | 241 | | 261 | |
| 141 | | 161 | | 181 | | 201 | | 221 | | 241 | | 261 | |
| 142 | | 162 | | 182 | | 202 | | 222 | | 242 | | 262 | |
| 142 | | 162 | | 182 | | 202 | | 222 | | 242 | | 262 | |
| 143 | | 163 | | 183 | | 203 | | 223 | | 243 | | 263 | |
| 143 | | 163 | | 183 | | 203 | | 223 | | 243 | | 263 | |
| 144 | | 164 | | 184 | | 204 | | 224 | | 244 | | 264 | |
| 144 | | 164 | | 184 | | 204 | | 224 | | 244 | | 264 | |
| 145 | | 165 | | 185 | | 205 | | 225 | | 245 | | 265 | |
| 145 | | 165 | | 185 | | 205 | | 225 | | 245 | | 265 | |
| 146 | | 166 | | 186 | | 206 | | 226 | | 246 | | 266 | |
| 146 | | 166 | | 186 | | 206 | | 226 | | 246 | | 266 | |
| 147 | | 167 | | 187 | | 207 | | 227 | | 247 | | 267 | |
| 147 | | 167 | | 187 | | 207 | | 227 | | 247 | | 267 | |
| 148 | | 168 | | 188 | | 208 | | 228 | | 248 | | 268 | |
| 148 | | 168 | | 188 | | 208 | | 228 | | 248 | | 268 | |
| 149 | | 169 | | 189 | | 209 | | 229 | | 249 | | 269 | |
| 149 | | 169 | | 189 | | 209 | | 229 | | 249 | | 269 | |
| 150 | | 170 | | 190 | | 210 | | 230 | | 250 | | 270 | |
| 150 | | 170 | | 190 | | 210 | | 230 | | 250 | | 270 | |
| 151 | | 171 | | 191 | | 211 | | 231 | | 251 | | 271 | |
| 151 | | 171 | | 191 | | 211 | | 231 | | 251 | | 271 | |
| 152 | | 172 | | 192 | | 212 | | 232 | | 252 | | 272 | |
| 152 | | 172 | | 192 | | 212 | | 232 | | 252 | | 272 | |
| 153 | | 173 | | 193 | | 213 | | 233 | | 253 | | 273 | |
| 153 | | 173 | | 193 | | 213 | | 233 | | 253 | | 273 | |
| 154 | | 174 | | 194 | | 214 | | 234 | | 254 | | 274 | |
| 154 | | 174 | | 194 | | 214 | | 234 | | 254 | | 274 | |
| 155 | | 175 | | 195 | | 215 | | 235 | | 255 | | 275 | |
| 155 | | 175 | | 195 | | 215 | | 235 | | 255 | | 275 | |
| 156 | | 176 | | 196 | | 216 | | 236 | | 256 | | 276 | |
| 156 | | 176 | | 196 | | 216 | | 236 | | 256 | | 276 | |
| 157 | | 177 | | 197 | | 217 | | 237 | | 257 | | 277 | |
| 157 | | 177 | | 197 | | 217 | | 237 | | 257 | | 277 | |
| 158 | | 178 | | 198 | | 218 | | 238 | | 258 | | 278 | |
| 158 | | 178 | | 198 | | 218 | | 238 | | 258 | | 278 | |
| 159 | | 179 | | 199 | | 219 | | 239 | | 259 | | 279 | |
| 159 | | 179 | | 199 | | 219 | | 239 | | 259 | | 279 | |
| 160 | | 180 | | 200 | | 220 | | 240 | | 260 | | 280 | |
| 160 | | 180 | | 200 | | 220 | | 240 | | 260 | | 280 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

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SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
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| 422 | | 442 | | 612 | | 632 | | 652 | | 672 | | 692 | |
| 423 | | 443 | | 613 | | 633 | | 653 | | 673 | | 693 | |
| 423 | | 443 | | 613 | | 633 | | 653 | | 673 | | 693 | |
| 424 | | 444 | | 614 | | 634 | | 654 | | 674 | | 694 | |
| 424 | | 444 | | 614 | | 634 | | 654 | | 674 | | 694 | |
| 425 | | 445 | | 615 | | 635 | | 655 | | 675 | | 695 | |
| 425 | | 445 | | 615 | | 635 | | 655 | | 675 | | 695 | |
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| 426 | | 446 | | 616 | | 636 | | 656 | | 676 | | 696 | |
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| 427 | | 447 | | 617 | | 637 | | 657 | | 677 | | 697 | |
| 428 | | 598 | | 618 | | 638 | | 658 | | 678 | | 698 | |
| 428 | | 598 | | 618 | | 638 | | 658 | | 678 | | 698 | |
| 429 | | 599 | | 619 | | 639 | | 659 | | 679 | | 699 | |
| 429 | | 599 | | 619 | | 639 | | 659 | | 679 | | 699 | |
| 430 | | 600 | | 620 | | 640 | | 660 | | 680 | | 700 | |
| 430 | | 600 | | 620 | | 640 | | 660 | | 680 | | 700 | |
| 431 | | 601 | | 621 | | 641 | | 661 | | 681 | | 701 | |
| 431 | | 601 | | 621 | | 641 | | 661 | | 681 | | 701 | |
| 432 | | 602 | | 622 | | 642 | | 662 | | 682 | | 702 | |
| 432 | | 602 | | 622 | | 642 | | 662 | | 682 | | 702 | |
| 433 | | 603 | | 623 | | 643 | | 663 | | 683 | | 703 | |
| 433 | | 603 | | 623 | | 643 | | 663 | | 683 | | 703 | |
| 434 | | 604 | | 624 | | 644 | | 664 | | 684 | | 704 | |
| 434 | | 604 | | 624 | | 644 | | 664 | | 684 | | 704 | |
| 435 | | 605 | | 625 | | 645 | | 665 | | 685 | | 705 | |
| 435 | | 605 | | 625 | | 645 | | 665 | | 685 | | 705 | |
| 436 | | 606 | | 626 | | 646 | | 666 | | 686 | | 706 | |
| 436 | | 606 | | 626 | | 646 | | 666 | | 686 | | 706 | |
| 437 | | 607 | | 627 | | 647 | | 667 | | 687 | | 707 | |
| 437 | | 607 | | 627 | | 647 | | 667 | | 687 | | 707 | |
| 438 | | 608 | | 628 | | 648 | | 668 | | 688 | | 708 | |
| 438 | | 608 | | 628 | | 648 | | 668 | | 688 | | 708 | |
| 439 | | 609 | | 629 | | 649 | | 669 | | 689 | | 709 | |
| 439 | | 609 | | 629 | | 649 | | 669 | | 689 | | 709 | |
| 440 | | 610 | | 630 | | 650 | | 670 | | 690 | | 710 | |
| 440 | | 610 | | 630 | | 650 | | 670 | | 690 | | 710 | |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
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| 711 | | 731 | | 751 | | 771 | | 791 | | 811 | | 831 | |
| 712 | | 732 | | 752 | | 772 | | 792 | | 812 | | 832 | |
| 712 | | 732 | | 752 | | 772 | | 792 | | 812 | | 832 | |
| 713 | | 733 | | 753 | | 773 | | 793 | | 813 | | 833 | |
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| 715 | | 735 | | 755 | | 775 | | 795 | | 815 | | 835 | |
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| 716 | | 736 | | 756 | | 776 | | 796 | | 816 | | 836 | |
| 716 | | 736 | | 756 | | 776 | | 796 | | 816 | | 836 | |
| 717 | | 737 | | 757 | | 777 | | 797 | | 817 | | 837 | |
| 717 | | 737 | | 757 | | 777 | | 797 | | 817 | | 837 | |
| 718 | | 738 | | 758 | | 778 | | 798 | | 818 | | 838 | |
| 718 | | 738 | | 758 | | 778 | | 798 | | 818 | | 838 | |
| 719 | | 739 | | 759 | | 779 | | 799 | | 819 | | 839 | |
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| 720 | | 740 | | 760 | | 780 | | 800 | | 820 | | 840 | |
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| 721 | | 741 | | 761 | | 781 | | 801 | | 821 | | 841 | |
| 722 | | 742 | | 762 | | 782 | | 802 | | 822 | | 842 | |
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| 724 | | 744 | | 764 | | 784 | | 804 | | 824 | | 844 | |
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| 725 | | 745 | | 765 | | 785 | | 805 | | 825 | | 845 | |
| 725 | | 745 | | 765 | | 785 | | 805 | | 825 | | 845 | |
| 726 | | 746 | | 766 | | 786 | | 806 | | 826 | | 846 | |
| 726 | | 746 | | 766 | | 786 | | 806 | | 826 | | 846 | |
| 727 | | 747 | | 767 | | 787 | | 807 | | 827 | | 847 | |
| 727 | | 747 | | 767 | | 787 | | 807 | | 827 | | 847 | |
| 728 | | 748 | | 768 | | 788 | | 808 | | 828 | | 848 | |
| 728 | | 748 | | 768 | | 788 | | 808 | | 828 | | 848 | |
| 729 | | 749 | | 769 | | 789 | | 809 | | 829 | | 849 | |
| 729 | | 749 | | 769 | | 789 | | 809 | | 829 | | 849 | |
| 730 | | 750 | | 770 | | 790 | | 810 | | 830 | | 850 | |
| 730 | | 750 | | 770 | | 790 | | 810 | | 830 | | 850 | |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 891 | |
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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 951 | |
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| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 971 | |
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SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 991 | | |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 1011 | | |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 1031 | | |
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| | 448 | Y | |
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| | 449 | Y | |
| | 449 | Y | |
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| | 450 | Y | |
| | 451 | Y | |
| | 451 | Y | |
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| | 452 | Y | |
| | 453 | Y | |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 454 | Y | |
| | 454 | Y | |
| | 455 | Y | |
| | 455 | Y | |
| | 456 | Y | |
| | 456 | Y | |
| | 457 | Y | |
| | 457 | Y | |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 474 | Y | |
| | 474 | Y | |
| | 475 | Y | |
| | 475 | Y | |
| | 476 | Y | |
| | 476 | Y | |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 494 | Y | |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 514 | Y | |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 594 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
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| | 1100 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 1101 | | Y |
| | 1101 | | Y |
| | 1102 | | Y |
| | 1102 | | Y |
| | 1103 | | Y |
| | 1103 | | Y |
| | 1104 | | Y |
| | 1104 | | Y |
| | 1105 | | Y |
| | 1105 | | Y |
| | 1106 | | Y |
| | 1106 | | Y |
| | 1107 | | Y |
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| | 1108 | | Y |
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| | 1109 | | Y |
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| | 1110 | | Y |
| | 1110 | | Y |
| | 1111 | | Y |
| | 1111 | | Y |
| | 1112 | | Y |
| | 1112 | | Y |
| | 1113 | | Y |
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| | 1114 | | Y |
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| | 1115 | | Y |
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| | 1116 | | Y |
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| | 1117 | | Y |
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| | 1118 | | Y |
| | 1118 | | Y |
| | 1119 | | Y |
| | 1119 | | Y |
| | 1120 | | Y |
| | 1120 | | Y |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : HRV - HRV

| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 1121 | Y |
| | 1121 | Y |
| | 1122 | Y |
| | 1122 | Y |
| | 1123 | Y |
| | 1123 | Y |
| | 1124 | Y |
| | 1124 | Y |
| | 1125 | Y |
| | 1125 | Y |
| | 1126 | Y |
| | 1126 | Y |
| | 1127 | Y |
| | 1127 | Y |
| | 1128 | Y |
| | 1128 | Y |
| | 1129 | Y |
| | 1129 | Y |
| | 1130 | Y |
| | 1130 | Y |
| | 1131 | Y |
| | 1131 | Y |
| | 1132 | Y |
| | 1132 | Y |
| | 1133 | Y |
| | 1133 | Y |
| | 1134 | Y |
| | 1134 | Y |
| | 1135 | Y |
| | 1135 | Y |
| | 1136 | Y |
| | 1136 | Y |
| | 1137 | Y |
| | 1137 | Y |
| | 1138 | Y |
| | 1138 | Y |
| | 1139 | Y |
| | 1139 | Y |
| | 1140 | Y |
| | 1140 | Y |

| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 1141 | Y |
| | 1141 | Y |
| | 1142 | Y |
| | 1142 | Y |
| | 1143 | Y |
| | 1143 | Y |
| | 1144 | Y |
| | 1144 | Y |
| | 1145 | Y |
| | 1145 | Y |
| | 1146 | Y |
| | 1146 | Y |
| | 1147 | Y |
| | 1147 | Y |
| | 1148 | Y |
| | 1148 | Y |
| | 1149 | Y |
| | 1149 | Y |
| | 1150 | Y |
| | 1150 | Y |
| | 1151 | Y |
| | 1151 | Y |
| | 1152 | Y |
| | 1152 | Y |
| | 1153 | Y |
| | 1153 | Y |
| | 1154 | Y |
| | 1154 | Y |
| | 1155 | Y |
| | 1155 | Y |
| | 1156 | Y |
| | 1156 | Y |
| | 1157 | Y |
| | 1157 | Y |
| | 1158 | Y |
| | 1158 | Y |
| | 1159 | Y |
| | 1159 | Y |
| | 1160 | Y |
| | 1160 | Y |

| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 1161 | Y |
| | 1161 | Y |
| | 1162 | Y |
| | 1162 | Y |
| | 1163 | Y |
| | 1163 | Y |
| | 1164 | Y |
| | 1164 | Y |
| | 1165 | Y |
| | 1165 | Y |
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| | 1166 | Y |
| | 1167 | Y |
| | 1167 | Y |
| | 1168 | Y |
| | 1168 | Y |
| | 1169 | Y |
| | 1169 | Y |
| | 1170 | Y |
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| | 1172 | Y |
| | 1172 | Y |
| | 1173 | Y |
| | 1173 | Y |
| | 1174 | Y |
| | 1174 | Y |
| | 1175 | Y |
| | 1175 | Y |
| | 1176 | Y |
| | 1176 | Y |
| | 1177 | Y |
| | 1177 | Y |
| | 1178 | Y |
| | 1178 | Y |
| | 1179 | Y |
| | 1179 | Y |
| | 1180 | Y |
| | 1180 | Y |

| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 1181 | Y |
| | 1181 | Y |
| | 1182 | Y |
| | 1182 | Y |
| | 1183 | Y |
| | 1183 | Y |
| | 1184 | Y |
| | 1184 | Y |
| | 1185 | Y |
| | 1185 | Y |
| | 1186 | Y |
| | 1186 | Y |
| | 1187 | Y |
| | 1187 | Y |
| | 1188 | Y |
| | 1188 | Y |
| | 1189 | Y |
| | 1189 | Y |
| | 1190 | Y |
| | 1190 | Y |
| | 1191 | Y |
| | 1191 | Y |
| | 1192 | Y |
| | 1192 | Y |
| | 1193 | Y |
| | 1193 | Y |
| | 1194 | Y |
| | 1194 | Y |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 1 | | [redacted] | 21 | | [redacted] | 41 | | [redacted] | 61 | | [redacted] | 81 | | [redacted] | 101 | | [redacted] | 121 | |
| | 1 | | | 21 | | | 41 | | | 61 | | | 81 | | | 101 | | | 121 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 2 | | | 22 | | | 42 | | | 62 | | | 82 | | | 102 | | | 122 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 3 | | | 23 | | | 43 | | | 63 | | | 83 | | | 103 | | | 123 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 4 | | | 24 | | | 44 | | | 64 | | | 84 | | | 104 | | | 124 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 5 | | | 25 | | | 45 | | | 65 | | | 85 | | | 105 | | | 125 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 6 | | | 26 | | | 46 | | | 66 | | | 86 | | | 106 | | | 126 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 7 | | | 27 | | | 47 | | | 67 | | | 87 | | | 107 | | | 127 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 8 | | | 28 | | | 48 | | | 68 | | | 88 | | | 108 | | | 128 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 9 | | | 29 | | | 49 | | | 69 | | | 89 | | | 109 | | | 129 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 10 | | | 30 | | | 50 | | | 70 | | | 90 | | | 110 | | | 130 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 11 | | | 31 | | | 51 | | | 71 | | | 91 | | | 111 | | | 131 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 12 | | | 32 | | | 52 | | | 72 | | | 92 | | | 112 | | | 132 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 13 | | | 33 | | | 53 | | | 73 | | | 93 | | | 113 | | | 133 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 14 | | | 34 | | | 54 | | | 74 | | | 94 | | | 114 | | | 134 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 15 | | | 35 | | | 55 | | | 75 | | | 95 | | | 115 | | | 135 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 16 | | | 36 | | | 56 | | | 76 | | | 96 | | | 116 | | | 136 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 17 | | | 37 | | | 57 | | | 77 | | | 97 | | | 117 | | | 137 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 18 | | | 38 | | | 58 | | | 78 | | | 98 | | | 118 | | | 138 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 19 | | | 39 | | | 59 | | | 79 | | | 99 | | | 119 | | | 139 | |
| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |
| | 20 | | | 40 | | | 60 | | | 80 | | | 100 | | | 120 | | | 140 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag |
|---|---|
| [redacted] | 141 |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 161 |
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| Trt. Bl. No nb | Repl. flag |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 221 |
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| Trt. Bl. No nb | Repl. flag |
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| [redacted] | 241 |
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| Trt. Bl. No nb | Repl. flag |
|---|---|
| [redacted] | 261 |
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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 281 | [redacted] | 301 | [redacted] | 321 | [redacted] | 341 | [redacted] | 361 | [redacted] | 381 | [redacted] | 401 |
| | 281 | | 301 | | 321 | | 341 | | 361 | | 381 | | 401 |
| | 282 | | 302 | | 322 | | 342 | | 362 | | 382 | | 402 |
| | 282 | | 302 | | 322 | | 342 | | 362 | | 382 | | 402 |
| | 283 | | 303 | | 323 | | 343 | | 363 | | 383 | | 403 |
| | 283 | | 303 | | 323 | | 343 | | 363 | | 383 | | 403 |
| | 284 | | 304 | | 324 | | 344 | | 364 | | 384 | | 404 |
| | 284 | | 304 | | 324 | | 344 | | 364 | | 384 | | 404 |
| | 285 | | 305 | | 325 | | 345 | | 365 | | 385 | | 405 |
| | 285 | | 305 | | 325 | | 345 | | 365 | | 385 | | 405 |
| | 286 | | 306 | | 326 | | 346 | | 366 | | 386 | | 406 |
| | 286 | | 306 | | 326 | | 346 | | 366 | | 386 | | 406 |
| | 287 | | 307 | | 327 | | 347 | | 367 | | 387 | | 407 |
| | 287 | | 307 | | 327 | | 347 | | 367 | | 387 | | 407 |
| | 288 | | 308 | | 328 | | 348 | | 368 | | 388 | | 408 |
| | 288 | | 308 | | 328 | | 348 | | 368 | | 388 | | 408 |
| | 289 | | 309 | | 329 | | 349 | | 369 | | 389 | | 409 |
| | 289 | | 309 | | 329 | | 349 | | 369 | | 389 | | 409 |
| | 290 | | 310 | | 330 | | 350 | | 370 | | 390 | | 410 |
| | 290 | | 310 | | 330 | | 350 | | 370 | | 390 | | 410 |
| | 291 | | 311 | | 331 | | 351 | | 371 | | 391 | | 411 |
| | 291 | | 311 | | 331 | | 351 | | 371 | | 391 | | 411 |
| | 292 | | 312 | | 332 | | 352 | | 372 | | 392 | | 412 |
| | 292 | | 312 | | 332 | | 352 | | 372 | | 392 | | 412 |
| | 293 | | 313 | | 333 | | 353 | | 373 | | 393 | | 413 |
| | 293 | | 313 | | 333 | | 353 | | 373 | | 393 | | 413 |
| | 294 | | 314 | | 334 | | 354 | | 374 | | 394 | | 414 |
| | 294 | | 314 | | 334 | | 354 | | 374 | | 394 | | 414 |
| | 295 | | 315 | | 335 | | 355 | | 375 | | 395 | | 415 |
| | 295 | | 315 | | 335 | | 355 | | 375 | | 395 | | 415 |
| | 296 | | 316 | | 336 | | 356 | | 376 | | 396 | | 416 |
| | 296 | | 316 | | 336 | | 356 | | 376 | | 396 | | 416 |
| | 297 | | 317 | | 337 | | 357 | | 377 | | 397 | | 417 |
| | 297 | | 317 | | 337 | | 357 | | 377 | | 397 | | 417 |
| | 298 | | 318 | | 338 | | 358 | | 378 | | 398 | | 418 |
| | 298 | | 318 | | 338 | | 358 | | 378 | | 398 | | 418 |
| | 299 | | 319 | | 339 | | 359 | | 379 | | 399 | | 419 |
| | 299 | | 319 | | 339 | | 359 | | 379 | | 399 | | 419 |
| | 300 | | 320 | | 340 | | 360 | | 380 | | 400 | | 420 |
| | 300 | | 320 | | 340 | | 360 | | 380 | | 400 | | 420 |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | 421 | | [redacted] | 441 | | [redacted] | 611 | | [redacted] | 631 | | [redacted] | 651 | | [redacted] | 671 | | [redacted] | 691 | |
| | 421 | | | 441 | | | 611 | | | 631 | | | 651 | | | 671 | | | 691 | |
| | 422 | | | 442 | | | 612 | | | 632 | | | 652 | | | 672 | | | 692 | |
| | 422 | | | 442 | | | 612 | | | 632 | | | 652 | | | 672 | | | 692 | |
| | 423 | | | 443 | | | 613 | | | 633 | | | 653 | | | 673 | | | 693 | |
| | 423 | | | 443 | | | 613 | | | 633 | | | 653 | | | 673 | | | 693 | |
| | 424 | | | 444 | | | 614 | | | 634 | | | 654 | | | 674 | | | 694 | |
| | 424 | | | 444 | | | 614 | | | 634 | | | 654 | | | 674 | | | 694 | |
| | 425 | | | 445 | | | 615 | | | 635 | | | 655 | | | 675 | | | 695 | |
| | 425 | | | 445 | | | 615 | | | 635 | | | 655 | | | 675 | | | 695 | |
| | 426 | | | 446 | | | 616 | | | 636 | | | 656 | | | 676 | | | 696 | |
| | 426 | | | 446 | | | 616 | | | 636 | | | 656 | | | 676 | | | 696 | |
| | 427 | | | 447 | | | 617 | | | 637 | | | 657 | | | 677 | | | 697 | |
| | 427 | | | 447 | | | 617 | | | 637 | | | 657 | | | 677 | | | 697 | |
| | 428 | | | 598 | | | 618 | | | 638 | | | 658 | | | 678 | | | 698 | |
| | 428 | | | 598 | | | 618 | | | 638 | | | 658 | | | 678 | | | 698 | |
| | 429 | | | 599 | | | 619 | | | 639 | | | 659 | | | 679 | | | 699 | |
| | 429 | | | 599 | | | 619 | | | 639 | | | 659 | | | 679 | | | 699 | |
| | 430 | | | 600 | | | 620 | | | 640 | | | 660 | | | 680 | | | 700 | |
| | 430 | | | 600 | | | 620 | | | 640 | | | 660 | | | 680 | | | 700 | |
| | 431 | | | 601 | | | 621 | | | 641 | | | 661 | | | 681 | | | 701 | |
| | 431 | | | 601 | | | 621 | | | 641 | | | 661 | | | 681 | | | 701 | |
| | 432 | | | 602 | | | 622 | | | 642 | | | 662 | | | 682 | | | 702 | |
| | 432 | | | 602 | | | 622 | | | 642 | | | 662 | | | 682 | | | 702 | |
| | 433 | | | 603 | | | 623 | | | 643 | | | 663 | | | 683 | | | 703 | |
| | 433 | | | 603 | | | 623 | | | 643 | | | 663 | | | 683 | | | 703 | |
| | 434 | | | 604 | | | 624 | | | 644 | | | 664 | | | 684 | | | 704 | |
| | 434 | | | 604 | | | 624 | | | 644 | | | 664 | | | 684 | | | 704 | |
| | 435 | | | 605 | | | 625 | | | 645 | | | 665 | | | 685 | | | 705 | |
| | 435 | | | 605 | | | 625 | | | 645 | | | 665 | | | 685 | | | 705 | |
| | 436 | | | 606 | | | 626 | | | 646 | | | 666 | | | 686 | | | 706 | |
| | 436 | | | 606 | | | 626 | | | 646 | | | 666 | | | 686 | | | 706 | |
| | 437 | | | 607 | | | 627 | | | 647 | | | 667 | | | 687 | | | 707 | |
| | 437 | | | 607 | | | 627 | | | 647 | | | 667 | | | 687 | | | 707 | |
| | 438 | | | 608 | | | 628 | | | 648 | | | 668 | | | 688 | | | 708 | |
| | 438 | | | 608 | | | 628 | | | 648 | | | 668 | | | 688 | | | 708 | |
| | 439 | | | 609 | | | 629 | | | 649 | | | 669 | | | 689 | | | 709 | |
| | 439 | | | 609 | | | 629 | | | 649 | | | 669 | | | 689 | | | 709 | |
| | 440 | | | 610 | | | 630 | | | 650 | | | 670 | | | 690 | | | 710 | |
| | 440 | | | 610 | | | 630 | | | 650 | | | 670 | | | 690 | | | 710 | |

SDD\RDE\ENABLE

Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 711 | |
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| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 731 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 751 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 771 | |
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| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 791 | |
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| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 811 | |
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| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 831 | |
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| | 850 | |
| | 850 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | | [redacted] | |
| 851 | | 871 | | 891 | | 911 | | 931 | | 951 | | 971 | |
| 851 | | 871 | | 891 | | 911 | | 931 | | 951 | | 971 | |
| 852 | | 872 | | 892 | | 912 | | 932 | | 952 | | 972 | |
| 852 | | 872 | | 892 | | 912 | | 932 | | 952 | | 972 | |
| 853 | | 873 | | 893 | | 913 | | 933 | | 953 | | 973 | |
| 853 | | 873 | | 893 | | 913 | | 933 | | 953 | | 973 | |
| 854 | | 874 | | 894 | | 914 | | 934 | | 954 | | 974 | |
| 854 | | 874 | | 894 | | 914 | | 934 | | 954 | | 974 | |
| 855 | | 875 | | 895 | | 915 | | 935 | | 955 | | 975 | |
| 855 | | 875 | | 895 | | 915 | | 935 | | 955 | | 975 | |
| 856 | | 876 | | 896 | | 916 | | 936 | | 956 | | 976 | |
| 856 | | 876 | | 896 | | 916 | | 936 | | 956 | | 976 | |
| 857 | | 877 | | 897 | | 917 | | 937 | | 957 | | 977 | |
| 857 | | 877 | | 897 | | 917 | | 937 | | 957 | | 977 | |
| 858 | | 878 | | 898 | | 918 | | 938 | | 958 | | 978 | |
| 858 | | 878 | | 898 | | 918 | | 938 | | 958 | | 978 | |
| 859 | | 879 | | 899 | | 919 | | 939 | | 959 | | 979 | |
| 859 | | 879 | | 899 | | 919 | | 939 | | 959 | | 979 | |
| 860 | | 880 | | 900 | | 920 | | 940 | | 960 | | 980 | |
| 860 | | 880 | | 900 | | 920 | | 940 | | 960 | | 980 | |
| 861 | | 881 | | 901 | | 921 | | 941 | | 961 | | 981 | |
| 861 | | 881 | | 901 | | 921 | | 941 | | 961 | | 981 | |
| 862 | | 882 | | 902 | | 922 | | 942 | | 962 | | 982 | |
| 862 | | 882 | | 902 | | 922 | | 942 | | 962 | | 982 | |
| 863 | | 883 | | 903 | | 923 | | 943 | | 963 | | 983 | |
| 863 | | 883 | | 903 | | 923 | | 943 | | 963 | | 983 | |
| 864 | | 884 | | 904 | | 924 | | 944 | | 964 | | 984 | |
| 864 | | 884 | | 904 | | 924 | | 944 | | 964 | | 984 | |
| 865 | | 885 | | 905 | | 925 | | 945 | | 965 | | 985 | |
| 865 | | 885 | | 905 | | 925 | | 945 | | 965 | | 985 | |
| 866 | | 886 | | 906 | | 926 | | 946 | | 966 | | 986 | |
| 866 | | 886 | | 906 | | 926 | | 946 | | 966 | | 986 | |
| 867 | | 887 | | 907 | | 927 | | 947 | | 967 | | 987 | |
| 867 | | 887 | | 907 | | 927 | | 947 | | 967 | | 987 | |
| 868 | | 888 | | 908 | | 928 | | 948 | | 968 | | 988 | |
| 868 | | 888 | | 908 | | 928 | | 948 | | 968 | | 988 | |
| 869 | | 889 | | 909 | | 929 | | 949 | | 969 | | 989 | |
| 869 | | 889 | | 909 | | 929 | | 949 | | 969 | | 989 | |
| 870 | | 890 | | 910 | | 930 | | 950 | | 970 | | 990 | |
| 870 | | 890 | | 910 | | 930 | | 950 | | 970 | | 990 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [redacted] 991 | | [redacted] 1011 | | [redacted] 1031 | | [redacted] 454 | Y | [redacted] 474 | Y | [redacted] 494 | Y | [redacted] 514 | Y |
| 991 | | 1011 | | 1031 | | 454 | Y | 474 | Y | 494 | Y | 514 | Y |
| 992 | | 1012 | | 1032 | | 455 | Y | 475 | Y | 495 | Y | 515 | Y |
| 992 | | 1012 | | 1032 | | 455 | Y | 475 | Y | 495 | Y | 515 | Y |
| 993 | | 1013 | | 1033 | | 456 | Y | 476 | Y | 496 | Y | 516 | Y |
| 993 | | 1013 | | 1033 | | 456 | Y | 476 | Y | 496 | Y | 516 | Y |
| 994 | | 1014 | | 1034 | | 457 | Y | 477 | Y | 497 | Y | 517 | Y |
| 994 | | 1014 | | 1034 | | 457 | Y | 477 | Y | 497 | Y | 517 | Y |
| 995 | | 1015 | | 1035 | | 458 | Y | 478 | Y | 498 | Y | 518 | Y |
| 995 | | 1015 | | 1035 | | 458 | Y | 478 | Y | 498 | Y | 518 | Y |
| 996 | | 1016 | | 1036 | | 459 | Y | 479 | Y | 499 | Y | 519 | Y |
| 996 | | 1016 | | 1036 | | 459 | Y | 479 | Y | 499 | Y | 519 | Y |
| 997 | | 1017 | | 1037 | | 460 | Y | 480 | Y | 500 | Y | 520 | Y |
| 997 | | 1017 | | 1037 | | 460 | Y | 480 | Y | 500 | Y | 520 | Y |
| 998 | | 1018 | | 1038 | | 461 | Y | 481 | Y | 501 | Y | 521 | Y |
| 998 | | 1018 | | 1038 | | 461 | Y | 481 | Y | 501 | Y | 521 | Y |
| 999 | | 1019 | | 1039 | | 462 | Y | 482 | Y | 502 | Y | 522 | Y |
| 999 | | 1019 | | 1039 | | 462 | Y | 482 | Y | 502 | Y | 522 | Y |
| 1000 | | 1020 | | 1040 | | 463 | Y | 483 | Y | 503 | Y | 523 | Y |
| 1000 | | 1020 | | 1040 | | 463 | Y | 483 | Y | 503 | Y | 523 | Y |
| 1001 | | 1021 | | 1041 | | 464 | Y | 484 | Y | 504 | Y | 524 | Y |
| 1001 | | 1021 | | 1041 | | 464 | Y | 484 | Y | 504 | Y | 524 | Y |
| 1002 | | 1022 | | 1042 | | 465 | Y | 485 | Y | 505 | Y | 525 | Y |
| 1002 | | 1022 | | 1042 | | 465 | Y | 485 | Y | 505 | Y | 525 | Y |
| 1003 | | 1023 | | 1043 | | 466 | Y | 486 | Y | 506 | Y | 526 | Y |
| 1003 | | 1023 | | 1043 | | 466 | Y | 486 | Y | 506 | Y | 526 | Y |
| 1004 | | 1024 | | 1044 | | 467 | Y | 487 | Y | 507 | Y | 527 | Y |
| 1004 | | 1024 | | 1044 | | 467 | Y | 487 | Y | 507 | Y | 527 | Y |
| 1005 | | 1025 | | 448 | Y | 468 | Y | 488 | Y | 508 | Y | 528 | Y |
| 1005 | | 1025 | | 448 | Y | 468 | Y | 488 | Y | 508 | Y | 528 | Y |
| 1006 | | 1026 | | 449 | Y | 469 | Y | 489 | Y | 509 | Y | 529 | Y |
| 1006 | | 1026 | | 449 | Y | 469 | Y | 489 | Y | 509 | Y | 529 | Y |
| 1007 | | 1027 | | 450 | Y | 470 | Y | 490 | Y | 510 | Y | 530 | Y |
| 1007 | | 1027 | | 450 | Y | 470 | Y | 490 | Y | 510 | Y | 530 | Y |
| 1008 | | 1028 | | 451 | Y | 471 | Y | 491 | Y | 511 | Y | 531 | Y |
| 1008 | | 1028 | | 451 | Y | 471 | Y | 491 | Y | 511 | Y | 531 | Y |
| 1009 | | 1029 | | 452 | Y | 472 | Y | 492 | Y | 512 | Y | 532 | Y |
| 1009 | | 1029 | | 452 | Y | 472 | Y | 492 | Y | 512 | Y | 532 | Y |
| 1010 | | 1030 | | 453 | Y | 473 | Y | 493 | Y | 513 | Y | 533 | Y |
| 1010 | | 1030 | | 453 | Y | 473 | Y | 493 | Y | 513 | Y | 533 | Y |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 534 | | Y |
| | 534 | | Y |
| | 535 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 554 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 574 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 594 | | Y |
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| | 596 | | Y |
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| | 1045 | | Y |
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| | 1046 | | Y |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 1061 | | Y |
| | 1061 | | Y |
| | 1062 | | Y |
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| | 1063 | | Y |
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| | 1066 | | Y |
| | 1067 | | Y |
| | 1067 | | Y |
| | 1068 | | Y |
| | 1068 | | Y |
| | 1069 | | Y |
| | 1069 | | Y |
| | 1070 | | Y |
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| | 1071 | | Y |
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| | 1078 | | Y |
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| | 1079 | | Y |
| | 1079 | | Y |
| | 1080 | | Y |
| | 1080 | | Y |

| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 1081 | | Y |
| | 1081 | | Y |
| | 1082 | | Y |
| | 1082 | | Y |
| | 1083 | | Y |
| | 1083 | | Y |
| | 1084 | | Y |
| | 1084 | | Y |
| | 1085 | | Y |
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| | 1087 | | Y |
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| | 1088 | | Y |
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| | 1089 | | Y |
| | 1089 | | Y |
| | 1090 | | Y |
| | 1090 | | Y |
| | 1091 | | Y |
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| | 1092 | | Y |
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| | 1093 | | Y |
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| | 1097 | | Y |
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| | 1099 | | Y |
| | 1099 | | Y |
| | 1100 | | Y |
| | 1100 | | Y |

| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 1101 | | Y |
| | 1101 | | Y |
| | 1102 | | Y |
| | 1102 | | Y |
| | 1103 | | Y |
| | 1103 | | Y |
| | 1104 | | Y |
| | 1104 | | Y |
| | 1105 | | Y |
| | 1105 | | Y |
| | 1106 | | Y |
| | 1106 | | Y |
| | 1107 | | Y |
| | 1107 | | Y |
| | 1108 | | Y |
| | 1108 | | Y |
| | 1109 | | Y |
| | 1109 | | Y |
| | 1110 | | Y |
| | 1110 | | Y |
| | 1111 | | Y |
| | 1111 | | Y |
| | 1112 | | Y |
| | 1112 | | Y |
| | 1113 | | Y |
| | 1113 | | Y |
| | 1114 | | Y |
| | 1114 | | Y |
| | 1115 | | Y |
| | 1115 | | Y |
| | 1116 | | Y |
| | 1116 | | Y |
| | 1117 | | Y |
| | 1117 | | Y |
| | 1118 | | Y |
| | 1118 | | Y |
| | 1119 | | Y |
| | 1119 | | Y |
| | 1120 | | Y |
| | 1120 | | Y |

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Randomisation list

ROTA-075 (A.31AUG2012)

Subjects from Group : Placebo - Placebo

| Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag | Trt. Bl. No nb | Repl. flag |
|---|---|---|---|---|---|---|---|
| [redacted] 1121 | Y | [redacted] 1141 | Y | [redacted] 1161 | Y | [redacted] 1181 | Y |
| 1121 | Y | 1141 | Y | 1161 | Y | 1181 | Y |
| 1122 | Y | 1142 | Y | 1162 | Y | 1182 | Y |
| 1122 | Y | 1142 | Y | 1162 | Y | 1182 | Y |
| 1123 | Y | 1143 | Y | 1163 | Y | 1183 | Y |
| 1123 | Y | 1143 | Y | 1163 | Y | 1183 | Y |
| 1124 | Y | 1144 | Y | 1164 | Y | 1184 | Y |
| 1124 | Y | 1144 | Y | 1164 | Y | 1184 | Y |
| 1125 | Y | 1145 | Y | 1165 | Y | 1185 | Y |
| 1125 | Y | 1145 | Y | 1165 | Y | 1185 | Y |
| 1126 | Y | 1146 | Y | 1166 | Y | 1186 | Y |
| 1126 | Y | 1146 | Y | 1166 | Y | 1186 | Y |
| 1127 | Y | 1147 | Y | 1167 | Y | 1187 | Y |
| 1127 | Y | 1147 | Y | 1167 | Y | 1187 | Y |
| 1128 | Y | 1148 | Y | 1168 | Y | 1188 | Y |
| 1128 | Y | 1148 | Y | 1168 | Y | 1188 | Y |
| 1129 | Y | 1149 | Y | 1169 | Y | 1189 | Y |
| 1129 | Y | 1149 | Y | 1169 | Y | 1189 | Y |
| 1130 | Y | 1150 | Y | 1170 | Y | 1190 | Y |
| 1130 | Y | 1150 | Y | 1170 | Y | 1190 | Y |
| 1131 | Y | 1151 | Y | 1171 | Y | 1191 | Y |
| 1131 | Y | 1151 | Y | 1171 | Y | 1191 | Y |
| 1132 | Y | 1152 | Y | 1172 | Y | 1192 | Y |
| 1132 | Y | 1152 | Y | 1172 | Y | 1192 | Y |
| 1133 | Y | 1153 | Y | 1173 | Y | 1193 | Y |
| 1133 | Y | 1153 | Y | 1173 | Y | 1193 | Y |
| 1134 | Y | 1154 | Y | 1174 | Y | 1194 | Y |
| 1134 | Y | 1154 | Y | 1174 | Y | 1194 | Y |
| 1135 | Y | 1155 | Y | 1175 | Y | | |
| 1135 | Y | 1155 | Y | 1175 | Y | | |
| 1136 | Y | 1156 | Y | 1176 | Y | | |
| 1136 | Y | 1156 | Y | 1176 | Y | | |
| 1137 | Y | 1157 | Y | 1177 | Y | | |
| 1137 | Y | 1157 | Y | 1177 | Y | | |
| 1138 | Y | 1158 | Y | 1178 | Y | | |
| 1138 | Y | 1158 | Y | 1178 | Y | | |
| 1139 | Y | 1159 | Y | 1179 | Y | | |
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| 1140 | Y | 1160 | Y | 1180 | Y | | |
| 1140 | Y | 1160 | Y | 1180 | Y | | |

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Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. No | Bl. nb | Repl. flag |
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Randomisation list

ROTA-075 (A.31AUG2012)

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Randomisation list

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Randomisation list

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Randomisation list

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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 2315 | |
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| Trt. No | Bl. nb | Repl. flag |
|---|---|---|
| [redacted] | 2355 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 2395 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 2435 | |
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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 2475 | |
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| Trt. No | Bl. nb | Repl. flag |
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Randomisation list

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| Trt. | Bl. No | nb | Repl. flag |
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Randomisation list

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OPV

| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 2825 | 2826 | |
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| | 2843 | 2844 | |
| | 2845 | 2846 | |
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| | 2849 | 2850 | |
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| | 2853 | 2854 | |
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| | 2857 | 2858 | |
| | 2859 | 2860 | |
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| | 2863 | 2864 | |

| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 2865 | 2866 | |
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| | 2879 | 2880 | |
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| | 2887 | 2888 | |
| | 2889 | 2890 | |
| | 2891 | 2892 | |
| | 2893 | 2894 | |
| | 2895 | 2896 | |
| | 2897 | 2898 | |
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| | 2903 | 2904 | |

| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
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| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
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| | 2999 | 3000 | |
| | 3001 | 3002 | |
| | 3003 | 3004 | |
| | 3005 | 3006 | |
| | 3007 | 3008 | |
| | 3009 | 3010 | |
| | 3011 | 3012 | |
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| | 3017 | 3018 | |
| | 3019 | 3020 | |
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| | 3023 | 3024 | |

| Trt. | Bl. No | nb | Repl. flag |
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| [redacted] | 3025 | 3026 | |
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Randomisation list

ROTA-075 (A.31AUG2012)

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| Trt. No | Bl. nb | Repl. flag |
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| [redacted] | 3105 | |
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| [redacted] | 3345 | |
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Randomisation list

ROTA-075 (A.31AUG2012)

OPV

| Trt. | Bl. No | nb | Repl. flag |
|---|---|---|---|
| [redacted] | 3385 | 3386 | 3387 | 3388 | 3389 | 3390 | 3391 | 3392 | 3393 | 3394 | 3395 | 3396 | 3397 | 3398 | 3399 | 3400 | 3401 | 3402 | 3403 | 3404 | 3405 | 3406 | 3407 | 3408 | 3409 | 3410 | 3411 | 3412 | 3413 | 3414 | 3415 | 3416 | 3417 | 3418 | 3419 | 3420 | 3421 | 3422 | 3423 | 3424 | |
| [redacted] | 3425 | 3426 | 3427 | 3428 | 3429 | 3430 | 3431 | 3432 | 3433 | 3434 | 3435 | 3436 | 3437 | 3438 | 3439 | 3440 | 3441 | 3442 | 3443 | 3444 | 3445 | 3446 | 3447 | 3448 | 3449 | 3450 | 3451 | 3452 | 3453 | 3454 | 3455 | 3456 | 3457 | 3458 | 3459 | 3460 | 3461 | 3462 | 3463 | 3464 | |
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| [redacted] | 3585 | 3586 | 3587 | 3588 | 3589 | 3590 | 3591 | 3592 | 3593 | 3594 | 3595 | 3596 | 3597 | 3598 | 3599 | 3600 | 3601 | 3602 | 3603 | 3604 | 3605 | 3606 | 3607 | 3608 | 3609 | 3610 | 3611 | 3612 | 3613 | 3614 | 3615 | 3616 | 3617 | 3618 | 3619 | 3620 | 3621 | 3622 | 3623 | 3624 | |
| [redacted] | 3625 | 3626 | 3627 | 3628 | 3629 | 3630 | 3631 | 3632 | 3633 | 3634 | 3635 | 3636 | 3637 | 3638 | 3639 | 3640 | 3641 | 3642 | 3643 | 3644 | 3645 | 3646 | 3647 | 3648 | 3649 | 3650 | 3651 | 3652 | 3653 | 3654 | 3655 | 3656 | 3657 | 3658 | 3659 | 3660 | 3661 | 3662 | 3663 | 3664 | |

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Randomisation list

ROTA-075 (A.31AUG2012)

OPV

| Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag | Trt. No | Bl. nb | Repl. flag |
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| | 3672 | | | 3712 | | | 3752 | | | 3792 | | | 3832 | | | 3872 | |
| | 3673 | | | 3713 | | | 3753 | | | 3793 | | | 3833 | | | 3873 | |
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| | 3680 | | | 3720 | | | 3760 | | | 3800 | | | 3840 | | | 3880 | |
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| | 3682 | | | 3722 | | | 3762 | | | 3802 | | | 3842 | | | 3882 | |
| | 3683 | | | 3723 | | | 3763 | | | 3803 | | | 3843 | | | 3883 | |
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| | 3701 | | | 3741 | | | 3781 | | | 3821 | | | 3861 | | | | |
| | 3702 | | | 3742 | | | 3782 | | | 3822 | | | 3862 | | | | |
| | 3703 | | | 3743 | | | 3783 | | | 3823 | | | 3863 | | | | |
| | 3704 | | | 3744 | | | 3784 | | | 3824 | | | 3864 | | | | |

# Audit Certificates

# AUDIT CERTIFICATE

## Study Number: ROTA 075 (113808)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Clinical studies are conducted by or on behalf of GlaxoSmithKline in accordance with Standard Operating Procedures, which conform to the requirements of international GCP guidelines (ICH Harmonised Tripartite Guidelines E6 for Good Clinical Practice, FDA 21CFR parts 50, 56 and 312).

During the conduct and reporting of this/these study(s), the following independent audits were performed by or on behalf of GlaxoSmithKline.

| Study Number | Type | Conducted by | Centre number | Country | Audit Date |
|---|---|---|---|---|---|
| 113808 | Investigator Site | GSK CDQA | [redacted] | China | 26-27 June, 2011 |

Clinical Development Quality Assurance hereby confirm that the audits detailed above were carried out in accordance with appropriate regulatory requirements and guidelines in order to assess compliance with the study protocol, ICH GCP, FDA 21CFR parts 314.50 and 601.2, appropriate standard operating procedures and policies.

**Name:** [redacted] **Date:** 11 October, 2012

**Role:** Manager, CDQA

**Clinical Development Quality Assurance**
**GlaxoSmithKline Research and Development**

## Documentation of statistical methods

Refer to the Study Report.

## Documentation of inter-laboratory standardisation methods and quality assurance procedures

Not applicable.

## Publications based on the study

Not applicable.

*This section contained journal publication(s), which are protected by copyright laws and therefore have been excluded.*

*This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*